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THERAPY PHYSICS BIOLOGY

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EIGHTH SYMPOSIUM NEURORADIOLOGICUM
PARIS

25—30 September 1967

The majority of the papers presented at the Symposium dealt with the diagnostic aspects of radiology and will be published in separate issues The papers published in the present issue belong to the therapy and biology sections Not all of the papers read at the Symposium have been submitted for publication in Acta Radiologica but the titles of these articles are included in the Table of Contents (arranged in alphabetical order according to first author s name) The present issue also contains the introductory contributions to the round table conference on glioblastoma multiforme and the subsequent discussion

RADIOTHERAPY AND RADIOBIOLOGY

ROUND TABLE CONFERENCE ON GLIOBLASTOMA MULTIFORME

List of Authors and Contributors to Discussion

FROM THE INSTITUTE OF NEUROBIOLOGY (DIRECTOR PROF H HYDEN), THE DEPARTMENT OF OTO LARYNGOLOGY (DIRECTOR PROF G HERBERTS) AND THE DEPARTMENT OF RADIOTHERAPY (DIRECTOR PROF M STRANDQVIST) GOTHENBURG, SWEDEN

QUANTITATIVE STUDIES ON THE RADIOSENSITIVITY OF SINGLE CELLS IN THE NERVOUS TISSUE

by

OLLE HALLEN ANDERS HAMBERGER BENGT ROSENGREN and HANS ROCKERT

The central nervous system formerly considered fairly radioresistant is known to respond to even extremely low doses of ionizing radiation Physiologic and chemical changes in brain tissue have been reported and effects on constituents and enzymes at the cellular level have been demonstrated by histochemical techniques (HALEY et coll 1962)

The specific response of the CNS to ionizing radiation comprises several phases an acute stage (the first weeks after irradiation) which is followed by more or less complete recovery A second stage starts in the fourth or fifth month after irradiation and lasts for years (ARNOLD et coll 1954) Unless the irradiation dose is quite high the acute stage passes with unspecific or absent morphologic changes

The present study was designed to elucidate the chemical events in nerve cells during the acute (first weeks) reaction to ionizing radiation before any morphologic changes have set in Since glial cells (BROWNSON et coll 1963) react to ionizing radiation differently from nerve cells the problem can only be approached via isolated nerve cells We applied a single dose of irradiation to investigate the reversible changes of the acute stage

List of Authors and Contributors to *Discussion*

Fig 2 Roentgen tube specimen mount and proportional detector A — anode B — filament C — 9 μ Al window D — specimen stage with aperture F — high voltage electrode F — specimen

The total organic mass succinoxidase activity, potassium permeability and RNA content were then determined in the following way

Mass determination The cells were placed on aluminium foils where they were dried (Fig 1) The analysis was performed with an integrating roentgen



Fig 1 Isolated nerve cells from the Deiters nucleus prepared on aluminium foils for mass determination

The caudal part of the brain of albino rabbits was irradiated and measurements on neurons from the lateral vestibular nucleus (N Deiters) were performed at intervals ranging from 3 hours to 3 weeks after single exposures of 2 000 and 3 000 R The total organic mass, the succinoxidase activity, the membrane permeability for potassium and the RNA content were recorded

Material and Methods

Albino rabbits were used, and the brain stem area was irradiated with roentgen rays under the following conditions 200 kV, 0 9 mm Cu HVL, 310 R min and 6 cm×4 cm field The animals were given a light barbiturate anaesthesia Single surface doses of 3 000 R and 2 000 R were given and the actual dose given to the brain stem was estimated to be about 90 per cent of the surface dose

The animals were killed 3 hours and 1 to 15 and 20 days after irradiation

Slices of the brain stem were cut and a flake of tissue was taken from that part of the nucleus which contains Deiters giant nerve cells The single nerve cells were then separated by hand dissection

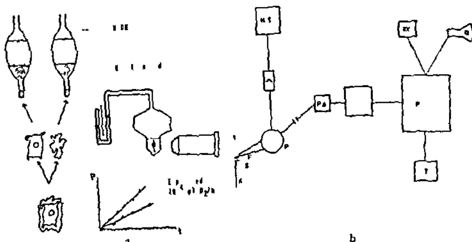


Fig 4 a) Schematic demonstration of the micro diver technique b) Schematic demonstration of roentgen fluorescence micro-analysis of potassium X — primary roentgen beam S — specimen P — proportional counter F — fluorescent radiation HT — high tension pA — praeamplifier A — amplifier PHA pulse height analyser xy — xy recorder O — oscilloscope T — typewriter

sorted out A curve with different peaks is seen on an oscilloscope (Fig 4b) Each peak represents one element and the height of the peak is proportional to the amount By using an internal standard the system is independent on variations in the primary beam Microdrops containing K and ^{131}I have been used as reference systems The volume of the drops have been determined by their known concentrations of ^{131}I with a scintillation counter Amounts down to 10^{-11} g K have been determined (LONG & ROCKERT 1963)

RNA determination The method of EDSTROM (1953) was used The cells were extracted with ribonuclease solution The extracts were evaporated to dryness and redissolved in buffered glycerol to form lens shaped droplets which were photographed at 257 Å The plates were scanned and the RNA calculated from the curve obtained The procedure is shown in Fig 5

Results

The results at 3 000 R are represented by the curves in Fig 6 There was an increase in the total mass the first day and a considerable increase occurred after 5 to 6 days The results from the 12th and 13th day indicated a return towards the normal level The means for the groups irradiated with 2 000 R and 1 000 R showed no significant difference from the control mean

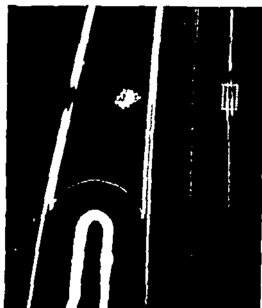


Fig 3 Nerve cell within microdiver for respiration analysis To the left enlargement of the area indicated to the right in the picture (From HAMBERGER 1963)

absorption technique A special roentgen tube operating at 3 kV is used The soft radiation leaves the tube through a 9 μ aluminium window and is collimated by a small aperture, 100 to 200 μ in diameter, on top of which the specimen is placed Passing the specimen, the cell, and, partly absorbed, the radiation is detected by a windowless proportional counter The total organic mass is then calculated from the absorption value (ROSENGREN 1959, HYDEN & ROSENGREN 1962) Fig 2 shows a cross section of the apparatus

Measurements of succinoxidase activity The neurons were transferred to a drop of incubation medium and each cell was introduced in a microdiver (Figs 3 and 4a) The succinoxidase activity was determined by measuring the oxygen consumption according to ZEUTHEN (1953), and expressed as 10^{-4} μl O_2 per sample per hour (HAMBERGER 1963)

Potassium determination The specimen is hit by roentgen rays from a Cosslett Nixon X ray microscope which can produce a high energy over a small spot A set of electron microscope apertures has been used as scatter trap On top of the last aperture the specimen is placed on a mylar foil Secondary roentgen rays, the fluorescent radiation, is generated spherically The energy of the fluorescent radiation is due to the elements present in the specimen and the intensity of each wavelength is proportional to the amount present in the specimen A sector of the fluorescent radiation is taken up by a proportional counter, and together with a multichannel pulse height analyzer different energies of the radiation can be

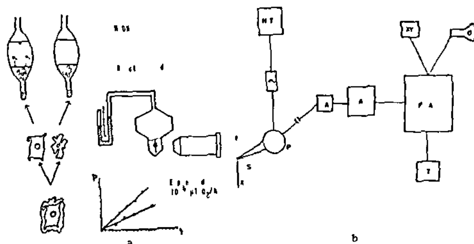


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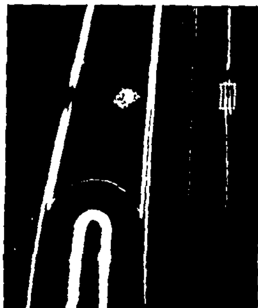


Fig. 3. Nerve cell within microdiver for respiration analysis. To the left enlargement of the area indicated to the right in the picture. (From HAMBERGER 1963.)

absorption technique. A special roentgen tube operating at 3 kV is used. The soft radiation leaves the tube through a 9 μ aluminium window and is collimated by a small aperture, 100 to 200 μ in diameter, on top of which the specimen is placed. Passing the specimen, the cell, and, partly absorbed, the radiation is detected by a windowless proportional counter. The total organic mass is then calculated from the absorption value (ROSENGREN 1959, HYDÉN & ROSENGREN 1962). Fig. 2 shows a cross section of the apparatus.

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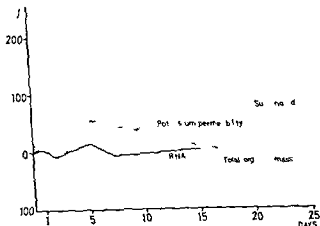


Fig 6 Total organic mass RNA content succinoxidase activity and potassium permeability of Deiters cell Results in per cent of control correlated to time after local irradiation with 3 000 R (HALLEN et coll 1967)

measurable effects are small below 2 000 R and a more definite change from the controls would be desirable especially owing to the variation in response that may occur in one and the same animal Even at this dose no obvious functional disturbances were encountered The morphologic changes in the nerve cell bodies were also insignificant during the first months (ARNOLD et coll 1954 SCHUMMELFELDER 1962 and ZEMAN et coll 1962)

The increase of the total cell mass is in accordance with DEVIKS (1962) observation that protein synthesis is increased after exposure to radiation The high level of respiration may also be due to the accelerated protein synthesis partly involving mitochondria Mitochondria are however morphologically and chemically very radiostable cell components and qualitative changes are probable only during the very early stage of increased succinoxidase activity The prompt and rapidly reversed increase in enzymatic activity in this stage is difficult to rationalize

The effects on potassium amounts indicate an action on cellular membranes The technique used here does not distinguish between cells having a low potassium content in vivo and cells losing their potassium more rapidly in vitro The intracellular potassium concentration is normally high after the radiation An increase in extracellular potentials of motoneurons following irradiation has been reported (SATO et coll 1962) and it is interesting that this effect reached its

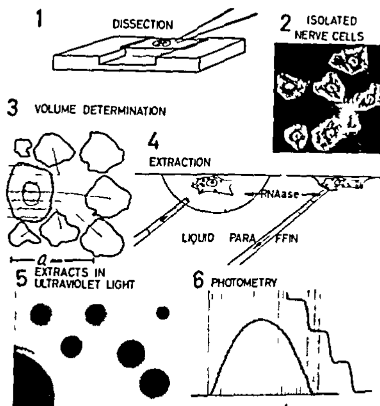


Fig 5 Schematization of the technique for RNA analysis

The succinoxidase activity after 3 000 R showed that the neurons developed an increase in respiration as early as a few hours after exposure to irradiation The relatively moderate change was followed by a more slowly rising level producing a peak of over 200 per cent increase 9 days after irradiation The effect of 2 000 R was considerably smaller

As can be seen from the curve, the potassium permeability increased so that the cell contained less potassium as early as 2 days after irradiation The peak value occurred 4 days later The cells gradually recovered but did not reach the level of the controls during the period studied

The RNA determination showed no impressive deviation from the normal value, but a slight increase after 5 days

Discussion

The largest groups of animals received an irradiation dose of 3 000 R This level was chosen after preliminary trials, mainly with lower doses As histologically demonstrated by BERG & LINDGREN (1958) for delayed radiation lesions the

ZUSAMMENFASSUNG

Das ganze organische Material das RNA Gehalt die Aktivitat der Succinoxydase und das Kaliumgehalt isolierter Deiters Riesennervenzellen wurden in Kaninchen nach Bestrahlung des Gehirnstammes studiert Auch die Aktivitat der Succinoxydase in den Homogenaten des Gehirnstammes wurde studiert Die Zellenreaktion wird im Verhaltnis zu verschiedener Arten von Zellenreizmitteln und experimenteller Bestrahlung von Nervenzellen diskutiert Die Schwellendosis messbarer Effekte wird in Relation zu den histologischen Befunden bei Spatbestrahlungslasionen gestellt

RÉSUMÉ

Les auteurs ont etudie sur des lapins apres irradiation du tronc cerebral le contenu organique total la teneur en ARN l activité de la succinoxydase et la teneur en potassium de cellules nerveuses geantes isolées de Deiters Ils ont aussi etudie l activité de la succinoxydase d homogenates de tronc cerébral Ils comparent les effets cellulaires de cette irradiation aux effets d autres types de stimulation cellulaire et d autres expérimentations d irradiation de cellules nerveuses Ils etudient les quantites de dose necessaires pour produire des effets mesurables et les rapprochent des constatations histologiques que l on trouve dans les radiolesions retardees

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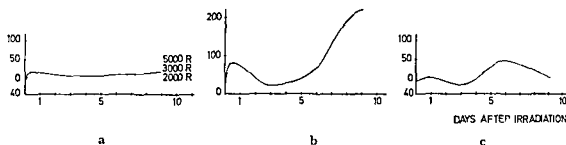


Fig 7 Succinoxidase activity versus time after irradiation a) Brain stem homogenate b) Nerve cells after 3 000 R c) Glial cells after 3 000 R

maximum about a week after the irradiation and then gradually decreased, but that the potentials still remained higher than the control values

In a recent paper, SEYMOUR et coll (1967) suggest that the effect of radiation of the frog sciatic nerve is probably leading to increased influx of sodium and efflux of potassium Our findings strongly support this suggestion since the measured efflux of potassium was demonstrated in isolated neurons

We have also made some studies of the succinoxidase activity in brain stem homogenates after various irradiation doses Fig 7 shows that the specific nerve cell response could possibly be reflected in the results of the homogenate but there is a considerable modification, probably because the changes in the glial cell respiration is quite different from those in the nerve cells

We have found a threshold for measurable effects after a single surface dose of about 3 000 R, which corresponds to the histologic changes after delayed radiation lesions demonstrated by BERG & LINDGREN (1958)

After using a correcting factor according to DU SAULT (1958) for the small volume irradiated in these experiments, the single dose in the brain stem could be referred to a clinical fractionated treatment course of 6 000 R in 30 days There also seems to be a threshold for radiation damage at this dose level which agrees with the histologic and chemical experimental observations mentioned here

SUMMARY

The total organic material the RNA content the succinoxidase activity and the potassium content of isolated Deiters giant nerve cells were studied in rabbits after irradiation of the brain stem area Succinoxidase activity in brain stem homogenates was also studied The cell response is discussed in relation to other types of cell stimulation and other radiation experiments with nerve cells The dose level for measurable effects is discussed in connection with histologic findings after delayed radiation lesions

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RADIOSENSITIZATION OF MALIGNANT BRAIN *TUMOURS WITH BROMOURIDINE* (THYMIDINE ANALOGUE)

by

TAKAO HOSHINO and KEIJI SANO

The treatment of malignant brain tumours has always attracted much attention in neurosurgery There are at present three ways of treating cerebral new growths namely surgical removal radiation therapy and chemotherapy Surgical treatment has its limitations and most gliomas and other malignancies are treated by partial removal decompression shunting procedures or a combination of all three Chemotherapy especially by means of continuous intracarotid infusion of anticancer drugs has been developed in our clinic since 1962 but satisfactory results have not yet been obtained Radiation therapy is effective in some tumours such as medulloblastoma ependymoma, pinealoma and pituitary adenoma but is rather ineffective in most other gliomas including glioblastoma Several analogues of thymidine have been recently synthesized, these strongly enhance the radiosensitivity of the cells thereby improving the effectiveness of radiation therapy

The authors have considered one of these compounds 5 bromo-2 deoxyuridine commonly called bromouridine or BUdR, as a radiosensitizer of malignant cerebral growths BUdR differs from thymidine only in that the methyl radical in the 5th position of the pyrimidine ring is replaced by bromide as shown below

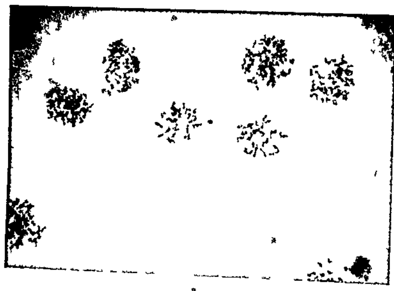
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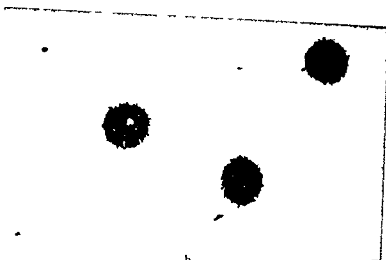
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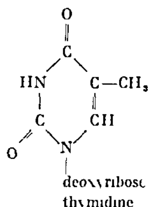


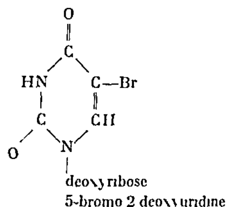
a



b

Fig 1 a) FL cells incubated for 2 days with 0 156 μg ml (specific activity of 1 μC ml) BUdR ³H b) Similar preparation of FL cells incubated for 2 days with the same amount of BUdR ³H and 1 μg/ml 5 FU * FL cell = strained fetus amnion cell





BUdR is incorporated only into the deoxyribonucleic acid (DNA) of dividing cells in place of thymidine As a result, the radiosensitivity of the cells having incorporated BUdR into their DNA increases about 2 to 3 times at single radiation exposures in vitro, as reported by DJORDJEVIC et coll (1960), KAPLAN et coll (1962) and others (1, 2, 8) BUdR has however almost neither cytocidal nor antimetabolic effects on the cells if they are not irradiated, a fact that has aroused keen interest from the viewpoint of radiotherapy Malignant tumours have a higher mitotic rate and accordingly are thought to be much more vigorous in synthesizing DNA than normal tissues The rate of uptake of the given BUdR into DNA should therefore be much higher in neoplasms than in surrounding normal tissues, and the destructive effect of radiation might be enhanced selectively in the malignant cells

Experimental studies No reports on the incorporation of BUdR into the cells of cerebral neoplasms have appeared The present authors wanted to confirm this incorporation with BUdR ^{3}H and human brain tumour cells cultured by a trypsinization monolayer method developed by them BUdR ^{3}H was added to the malignant cells cultured in the medium and autoradiography was carried out after 5 days of incubation The black grains were found to be concentrated at the position of nuclei of cells from e g glioblastoma, astroblastoma, astrocytoma ependymoblastoma, ependymoma, oligodendroglioma meningioma and meningosarcoma The labelling index of the BUdR ^{3}H of these tumours was checked at the same time and proved to be about the same as that of thymidine ^{3}H, this fact seemed to indicate that BUdR was taken up by cells dividing at the same rate as thymidine (16 17)

Subsequently, it could be shown that the cerebral tumour cells cultured with BUdR were much more sensitive to irradiation than those cultured without BUdR The method was as follows After having obtained a good proliferation

greater in the nuclei of the cells that were incubated with BUdR and 5 FU The rate of BUdR incorporation into cell nuclei, resulting from the addition of these antimetabolites appears from Table I

This finding may be explained by assuming that not all the tumour cells take up BUdR when preparing for mitosis because they can synthesize the thymidine necessary for duplicating their DNA However if this biosynthetic mechanism is inhibited by a small amount of antimetabolites the dividing cells will be forced to incorporate a thymidine analogue in the present instance the BUdR supplied in order to duplicate their DNA (4)

'BAR therapy

Based on the experimental results the authors have evolved the method of BUdR antimetabolite continuous intra arterial infusion radiation therapy, termed BAR therapy (10 16 17)

The advantages of the method in the treatment of malignant cerebral tumours with BUdR as a radiosensitizer are as follows (1) such tumours are usually solitary and rarely metastasize (2) the surrounding nerve cells have no mitotic ability and consequently hardly ever incorporate BUdR into their DNA (3) the normal brain tissue is supposed to be protected from the BUdR admini tered by the blood brain barrier whereas the tumour cells are exposed to this drug becau e of a breakdown of this barrier (4) intra arterial infusion therapy of the drug is easy

Intra arterial infusion of BUdR is necessary not only for obtaining a high amount of BUdR in the malignant tissue but also for avoiding dehalogenation of BUdR by the liver (12 13) More than 90 per cent of BUdR is dehalogenated in the liver within one hour of its intravenous injection This constitutes another advantage because the side effects of the drug can be minimized after it reaches the general circulation

The principle of the present method consists of administering 600 to 1 000 mg/day BUdR in adults together with a small amount of antimetabolite (e g 1 0 to 5 0 mg methotrexate or 3 0 to 5 0 mg 5 FU daily) by means of continuous intra arterial infusion and simultaneous radiation therapy Continuous infusion of these drugs is necessary—they must be administered continuously since the mitos s of the tumour cells takes place at random The problem is the duration of continuous infusion. The right answer to this question is to infuse for more than one generation time of the tumour cells so that all such cells can incorporate BUdR into their DNA It is however difficult to determine the true generation time of the various brain tumours At first the authors infused BUdR for periods

Table 1

Grade of the incorporation of ³H BUdR affected by antimetabolites

Concentration	Antimetabolites		
	Mtx	5 FU	FUdR
0.1 mg/ml	++	+++	+++
0.001 mg/ml	++	+++	++

Grain index

$$\frac{\text{Number of grains in the nuclei with antimetabolites in the medium}}{\text{Number of grains in the nuclei without antimetabolites in the medium}}$$

Mtx = methotrexate   ++ means 3—5   +++ means 5—10

of cells in culture, 10 to 40 µg ml BUdR were added to the medium and the bottles were incubated at 37° C for the period corresponding to the generation time of the cells obtained from the labelling index of the thymidine ³H The bottles were irradiated with 500 to 8 000 R in serially divided bands Control bottles without BUdR were also irradiated at the same time Following the irradiation, the bottles were incubated at 37° C for a further 7 to 20 days The materials were then fixed and stained The effects of the irradiation were judged mainly on the basis of the population of cells and their morphologic changes as compared with controls These experiments were possible since constant good growth had been obtained by the trypsinization monolayer technique in primary cultures of cerebral tumours (16, 17) The authors would like to emphasize that there was no inhibitory effect of the BUdR itself on the cells in vitro even in a long term culture of more than one hundred days

The amount of BUdR incorporated into the tumour cells was found, as previously, to be proportional to the amount of BUdR given in the medium The authors assume that the susceptibility of the cells to irradiation is related to the amount of BUdR incorporated into the cells, as reported by others (11) To radiosensitize brain tumour cells it might therefore be considered necessary to facilitate the incorporation of BUdR into the malignant cells by administering large doses of BUdR This is however impractical The authors therefore aimed at achieving maximal incorporation of BUdR into the cells with minimal doses and found that a small amount of an antimetabolite such as methotrexate, 5 fluorouracil (5 FU) or 5 fluoro-2′ deoxyuridine, enhanced the uptake of BUdR into the cell nuclei in vitro (16) Fig 1a is an autoradiogram of FL cells after their incubation for 2 days with 0 156 µg ml BUdR ³H, Fig 1b shows a parallel preparation of FL cells incubated for 2 days with the same amount of BUdR ³H and in addition 1 µg ml 5 FU It is seen that the number of grains is remarkably

Table 2

Follow up of cases

		Cases	Discontinued	Months 0–6	7–12	13–18	19–24	Over 2 years
Highly malignant Glioma	Alive	9	0	3	2	1	2	1
	Dead	5	4	0	1	0	0	0
Less malignant Glioma	Alive	6	0	2	2	2	0	
	Dead	0	0	0	0	0	0	
Meningosarcoma	Alive	4	0	1	0	1	0	2
	Dead	0	0	0	0	0	0	0
Metastatic tumor	Alive	1	1	0	0	0	0	0
	Dead	1	1	0	0	0	0	0
Other malignant tumours	Alive	4	1	2	1	0	0	0
	Dead	0	0	0	0	0	0	0
Total	Alive	24	2	8	5	4	2	3
	Dead	6	5	0	1	0	0	0

tumours (1 anaplastic papilloma of the choroid plexus 1 melanoma 1 scalp skull cancer 1 unverified thalamic tumour) two metastatic tumours

The total amount of BUdR administered to each patient varied from 9 000 to 34 000 mg and the total dose of irradiation was 5 000 to 6 000 R or more It is difficult to evaluate the effects of this therapy only by neurologic improvement because they are dependent on the location or size of the tumour and the neurologic deficits elicited by the destruction of nerve cells already present The roentgenologic signs i e at carotid angiography and pneumography, were always better following the treatment Two cases were re-examined after the BAR therapy had been completed and macroscopically as well as microscopically no residual malignant cells were detected at biopsy

As for the laboratory examinations during BAR therapy, there were no remarkable changes in the number of red blood cells and the amount of hemoglobin The number of white blood cells however decreased rather quickly when BUdR and methotrexate were infused at the same time though they recovered after the methotrexate supply had been cut off (Fig 2) Although the

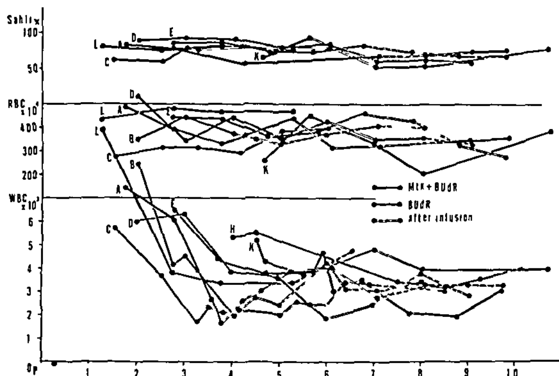


Fig 2 Blood counts during BAR therapy Rapid decrease of white blood cells when BUdR and methotrexate were infused at the same time Mtx = methotrexate op = operation Sahli = percentage of hemoglobin content as compared with the normal control (100% = 16 g/dl hemoglobin)

of 3 to 4 weeks in glioblastoma cases and for 4 to 6 weeks in cases of astrocytoma, with due consideration of the concept of generation time More recently they have been trying continuous infusion for up to 6 weeks, adjusting the duration to the malignancy of the tumour (e g glioblastoma more than 4 weeks, oligodendroglioma more than 6 weeks) It is their experience that BUdR produces practically no serious side effects

The authors usually perform decompressive craniotomy and remove a part of the tumour The pathologic diagnosis having been made a siliconized polythene tube of 1 4 mm inner diameter is inserted into the internal carotid artery, and continuous infusion is carried out by means of a small pump Radiation therapy follows 7 to 14 days after the commencement of the continuous infusion

This treatment has been applied in 30 cases as follows

Fourteen highly malignant gliomas (11 glioblastomas, 2 oligodendroblastomas, 1 ependymoblastoma) six less malignant gliomas (3 oligodendrogliomas 2 ependymomas 1 astrocytoma) four meningosarcomas four other malignant

A follow up of the cases is presented in Table 2 Five cases were lost during the BAR therapy Post mortem examination of these cases indicated that death was due to general weakness incidental cerebral hemorrhage apparently unconnected with the therapy, or tentorial herniation due to involvement of the uncus itself In two cases the therapy had to be discontinued in one because of severe infection of the catheterized region and in the other, a case of metastatic carcinoma because of the appearance of metastases on the opposite side The other 23 cases were discharged in better condition than before treatment One case of a 60 year old man with glioblastoma died 5 months after discharge from acute bronchopneumonia unassociated with the tumour The remaining 22 cases have been checked monthly in the out patient clinic and none so far has had signs of recurrence

Discussion

It is important, though difficult to determine the accurate development time of cerebral tumours in vivo It is important to know since the duration of the continuous infusion should be based on the generation time The authors have been studying the generation time of various brain tumours in vitro by three methods (3 17 18) and found that even in glioblastomas the time differed from 2 to 3 days with the roller tube culture method to 20 to 30 days with the bloc immersion method a recent report by KURY et coll (1965) gave however a much shorter generation time by the same bloc immersion method There is also evidence that not all the tumour cells have the ability of cell division nor have they the same generation time The data must therefore be accepted with some caution and the duration of infusion in glioblastoma cases should for safety be more than four weeks

Theoretically irradiation should take place after the termination of the infusion therapy because irradiation may depress the mitosis of the cells This is however rather difficult to adhere to in practice for the reason that the patients may have to be admitted to hospital for quite a long time Therefore the authors have started the radiation therapy 7 to 14 days after the commencement of infusion

Antimetabolites are used in this BAR therapy only for facilitating the incorporation of the BUdR into malignant cells and not for their intensification of the irradiation effects The doses of methotrexate and 5 Fu in this therapy are less than one tenth of the ordinary doses administered as anticancer drugs As shown in Table 1 the incorporation-enhancing effects of the antimetabolites in vitro were apparent even for a concentration of 1 ug/ml of the medium The authors still have not studied such effects in vivo but determined the daily dose of anti



Fig 3 Onychomadesis of finger nails (6 months after the therapy)

daily dose of methotrexate was small, the decrease in the number of white blood cells seemed to be accelerated by the simultaneous administration of BUdR Anyhow, BUdR itself had almost no depressive action on the hematopoietic system Other laboratory findings, such as the serum protein serum urea, serum electrolytes, and the results of liver function tests, excepting the values for the serum GOT and GPT, were within normal limits during and after the BAR therapy These values increased during the BAR therapy but soon returned to the normal range without any special treatment The effects of the therapy on the pressure of the cerebrospinal fluid was as follows In general, the pressure gradually decreased, although sometimes it temporarily increased at the beginning of radiotherapy These observations suggest that decompressive craniectomy prior to the therapy might be recommended Some of the patients still had severe bulging at the craniectomized area even at the end of the treatment but it usually disappeared in two to three months

As far as side effects of BUdR are concerned, depilation of the eyebrow as well as more severe epilation and radiodermatitis on the catheterized side of the forehead occurred when radiation was given to cover the forehead of the patient This may be explained as follows The forehead is fed by the internal carotid artery consequently the skin of the forehead was radiosensitized by BUdR The skin changes, however, did not develop as far as to ulceration, probably because the irradiation was applied with multiple portals Another side effect is worthy of mention This appeared two to three months after the therapy Onychomadesis of the finger nails as depicted in Fig 3 was very common although new nails soon replaced the old one This phenomenon sometimes appeared also in the toe nails

SUMMARY

Bromouridine which is known to radiosensitize bacterial and malignant cells was shown to be incorporated into the nuclei of cultured human cerebral neoplasm cells Its uptake in vitro was enhanced by the addition of a small amount of an antimetabolite such as methotrexate or 5 FU The authors describe the details of BAR therapy for malignant cerebral growths based upon this principle and discuss the results

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Dass die Radiosensitivitat der Bakterienzellen und malignen Zellen bei dem Bromuridin erhoht wird ist bekannt und es wurde gezeigt dass diese Substanz in den Kern der Zell kulturen von menschlichen Gehirntumoren eindringt Die Aufnahme der Substanz in vitro konnte bei Verabreichung kleiner Mengen von einem Anti Stoffwechselprodukt wie z B Methotrexat oder 5 FU verbessert werden Die auf diesem Prinzip basierte BAR Therapie bei Gehirngeschwulsten wird beschrieben und die Ergebnisse werden diskutiert

RÉSUMÉ

Les auteurs ont montre que la bromo uridine dont on sait qu elle sensibilise aux radiations les cellules bactériennes et les cellules malignes est incorporee dans les noyaux d cellules de neoplasmes cérébraux humains en culture Sa fixation in vitro est augmentee par l'addition de petites quantites d un antimétabolite tel que le methotrexate ou le 5 FU Les auteurs décrivent les détails de la BAR therapie (perfusion intra arterielle continue de bromo-uridine et d'antimétabolite associes a la radiothérapie pour les tumeurs cerebrales et etudient ses résultats

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metabolites as 1.5 to 5.0 mg methotrexate, or 3.0 to 5.0 mg 5-FU, with the blood plasma, estimated at 2 to 3 litres, regarded as the medium of tissue culture. The adequate daily dosage of antimetabolites must be determined in a future study.

The effects of the BUdR that is incorporated into normal dividing cells should be checked. Although BUdR is reported to be destroyed quickly by the liver so that only a small amount passes into the general circulation, an accumulation of side effects of any small amount of BUdR must not be neglected, since the treatment usually continues for more than 4 weeks. One obvious sign of such accumulation is onychomadesis of finger nails, as mentioned earlier. Some authors have also reported the mutagenicity of BUdR in prenatal animals (6, 9, 15). However, as far as acute intoxication by BUdR is concerned the amount of BUdR that the present authors have been administering to patients has been harmless. *Experiments have revealed that the LD_{50} of BUdR administered intra*venously to ICL JCL male mice, four weeks postnatal, was 2,700 mg/kg. The most effective and still harmless daily dose should, however, also be determined in the future.

BAR therapy requires long-term continuous intra-arterial infusion and this might be expected to lead to various complications. Fortunately, the method employed by the present authors has proved successful and most of the patients have been able to complete the proposed course of continuous infusion. The only complication that had to be dealt with was local infection of the skin through which the catheter was guided. This occurred in four out of 30 cases; in two of which an abscess developed at the site, after this had been controlled with antibiotics, a mycotic spurious aneurysm was found at the common carotid artery; in both cases this was successfully resected.

Other possible complications, such as cerebral thrombosis or occlusion of the carotid artery, were not experienced. In one case in which the catheter was inserted into the vertebral artery occlusion of this artery was recognized two weeks after the insertion. This occlusion may be ascribed to the catheter having been too large for the arterial lumen.

BAR therapy seems to promise good for the future as a means of treating malignant cerebral growths, although for a definite evaluation a long-term follow-up and control of the results would seem to be needed.

Acknowledgements

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ANATOMIC STUDIES OF THE DISTRIBUTION AND EFFECTS OF INTRATHECAL RADIOACTIVE GOLD

by

STEPHEN A KIEFFER EMANUEL M STADLAN and GIULIO J D ANGIO

A new regimen for the treatment of patients with tumors of the central nervous system that tend to seed via the cerebrospinal fluid pathways has been under study at the University of Minnesota hospitals (KIEFFER et coll 1966) This combines bolus myelography (MARTIN et coll 1966) external radiotherapy of the central nervous system and irradiation from an internal source i e a beta emitting radionuclide introduced intrathecally The rationale for this regimen has been described in detail elsewhere (D ANGIO et coll) Briefly its aim is to deliver tumoricidal doses of radiation to the leptomeningeal surfaces of the brain and spinal cord while sparing the underlying parenchyma

Radioactive ^{198}Au (Aureotope Squibb) was selected as the beta emitter This agent is readily available commercially in a sterile aqueous colloidal suspension which is stable and can be diluted with water normal saline or cerebrospinal fluid Its other advantages include (1) a short half life (2 7 days), (2) emission of a 0 97 MeV beta particle accounting for the great majority of the dose which therefore is limited to only the most superficial tissues and (3) gamma rays which are also emitted during decay allowing external monitoring of the flow and distribution of the isotope

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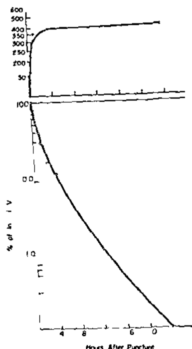


Fig 1

Upper graph External scintillation counts over the lumbar region of a dog injected with 5 mCi ^{198}Au into the lateral ventricle Rapid rise in count rate in the first hour after injection By 2 hours after injection the count rate in the lumbar region has approached its maximum

Lower graph Activity of 0.5 ml aliquots of cerebrospinal fluid withdrawn from the cisterna magna in another dog injected with 5 mCi ^{198}Au into the lateral ventricle Rapid fall in cisterna magna activity over the initial 2 hours

was placed about 1 cm lateral to the midline in the midportion of the parietal bone A polyethylene metal catheter needle combination was passed inferiorly and laterally in increments of 1 to 2 mm the obturator being removed after each advance of the needle until cerebrospinal fluid was obtained In several cases no fluid was obtained on advancing the needle to a depth of 5 to 6 cm the metal needle was then removed and slow retraction of the catheter usually resulted in a position where good flow of fluid was obtained Occasionally a second needle passage at a different angle was required

A dose of 5 mCi of colloidal ^{198}Au was then injected into the cerebrospinal fluid Usually sufficient normal saline solution or cerebrospinal fluid was mixed with the radionuclide to produce a 2 to 3 ml aliquot for injection Barbotage was not employed

The catheter was then removed and the burr hole sealed with bone wax The dogs were positioned on a flat board with the head end elevated 30 to 45 degrees above the horizontal They were then rotated around the longitudinal axis with 15 minutes spent in each of four positions (prone supine and both lateral decubiti)

Table

Experimental studies with intrathecal colloidal gold leptomeningeal vascular reaction

Time from injection to sacrifice	Number of animals	Radioactive gold			Number of animals	Non radioactive gold		
		0	1—2+	3—4+		0	1+	4+
2 days	2	2						
7 days	2	2						
2 weeks	5	1	4 (3)		[illegible]	2	3	
4 weeks	1			1				
2 months	5		1	4	[illegible]	3	1	1
6 months	2			2 (2)				
12 months	1		1					
18 months	1			1	2			2
Total	19	5	[illegible]	9	12	[illegible]	4	3

0 no change 1+ minimal 2+ mild 3+ moderate 4+ severe Parentheses indicate number of animals with more widespread leptomeningeal inflammatory cell infiltration No animals given non radioactive gold showed a 2+ or 3+ leptomeningeal vascular reaction

The present study, utilizing intrathecal radiogold in the laboratory animal, was undertaken to determine whether deleterious effects upon neural tissues would follow such treatment This information was needed before systematic clinical trials could be started

Material and Method

A total of 31 large dogs all of one breed (German Shepherd) were included in this study Initially, the radioactive material was to be introduced via a lumbar puncture in order to duplicate the route envisioned for man However, the great length of the spinal cord in the dog (extending down to the seventh or eighth lumbar vertebra) and the rather narrow spinal canal results in a narrow subarachnoid space in the lumbar region Preliminary studies, utilizing iodophenyl undecylate (Pantopaque, Lafayette) to verify the location of the injected bolus revealed that injection into the subarachnoid space could not be attained consistently via the lumbar route Although others have reported success with cisternal puncture, this method was also found to be too uncertain

Accordingly, an alternative method, injection into the lateral ventricle was selected The animal was anesthetized with intravenous secobarbital A burr hole



Fig 3 Autoradiograms of thin sections of the brain of a dog sacrificed ? days after intraventricular instillation of 5 mCi of ^{198}Au The upper two sections are from the frontal region and the lower two from the parietal region There is evidence of radioactivity over the convexities with hot areas in sulci and especially in the basilar cisterns

Results

All of the animals tolerated the procedure well A few developed mild fever and superficial wound infections but there were no clinically evident cases of meningitis encephalitis or systemic infection No gross neurologic deficit was present in any animal at the time of sacrifice

There was in all cases a rapid distribution of the radioactivity following introduction of the radioactive material into the cerebral ventricle A considerable portion of the radioactivity as monitored by external scintillation counting (Fig 1) and scintiphotos (Fig 2) was found in the cisterns of the posterior fossa and in the cervical and upper thoracic subarachnoid space during the first hour After 2 hours count rates had achieved maximal levels in the cervical and lumbar regions Activity of samples of cerebrospinal fluid withdrawn at intervals from the cisterna magna of the animal with the indwelling catheter fell off at a rapid rate during the first two hours and then declined very slowly thereafter (Fig 1)

The rapid falloff in cerebrospinal activity appears to reflect not only the passage of the colloid in a caudal direction but also the adherence (plating out) of the isotope to leptomeningeal surfaces of the brain and spinal cord External scintillation counts over the lumbar region in the same animal showed rapid rise over the first two hours and a much slower rise over the remainder of the 24 hour period Although the spleen and liver were routinely surveyed with both the scintillation camera and external scintillation counter no radioactivity could be detected in these organs in any animal

Autoradiograms of 5 mm thick sections of the brain and spinal cord from dogs sacrificed within the first week of life showed a circumferential distribution of the radionuclide along leptomeningeal surfaces (Fig 3) Relatively high activity was found in the basilar cisterns Ependymal surfaces of the ventricles did not retain

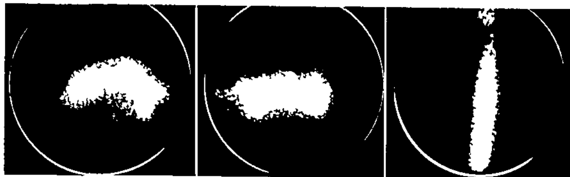


Fig 2 Scintillation photographs made with the Anger camera approximately 1 hour after intraventricular injection of 5 mCi of ^{198}Au *Left* lateral view of the head *Center* taken at the same time with the scintillation crystal above the head Both of these photos demonstrate diffuse activity throughout subarachnoid spaces and cisterns of the head without demonstrable residual activity in the ventricular system *Right* p a view of the cervical region obtained a few minutes later

The first eight dogs so treated were followed by frequent scintillation camera studies as well as external counting with a portable scintillation counter to monitor the redistribution of the radionuclide When the scintiphotos were seen to correlate closely with the external counts, only the latter method was employed in the remaining animals

Following this procedure, the animals were kept under close surveillance by qualified personnel under the supervision of a veterinarian They were sacrificed at intervals according to a schedule designed to demonstrate any early or late changes in the central nervous system Twelve of the 31 animals received a similar volume of the nuclide which had been allowed to decay through at least ten half lives Such a preparation (hereafter referred to as cold gold) would have a total radioactivity which would be negligible (1 4096 of the original activity) Each of the other 19 animals each received 5 mCi of ^{198}Au (see Table)

After sacrifice 1 cm long sections of the midcervical, mid and low thoracic, and lumbosacral spinal cord and roots were removed The entire brain was also removed These specimens were examined following fixation in a 10 % formalin solution

A slightly different procedure was followed in one additional large dog of the Vizla breed A catheter was introduced into the cisterna magna and secured in this location Following instillation of ^{198}Au into the ventricle aliquots of cerebro-spinal fluid were withdrawn at frequent intervals over a 24 hour period and assayed for radioactivity in a well counter At the same times external counts were made over a fixed site in the mid lumbar region



Fig 5 Dorsal root of thoracic spinal cord in animal sacrificed 18 months following radio gold Nerve roots normal moderate accumulation of lymphocytes and histiocytes in wall of leptomeningeal vein

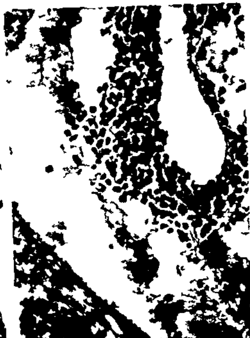


Fig 6 Diffuse meningeal infiltration in an imal sacrificed 2 weeks following radiogold Cerebellar leptomeninges and leptomeningeal veins infiltrated by moderate numbers of lymphocytes associated with histiocytic cell proliferation small numbers of eosinophiles and plasma cells also present in infiltrate extension of infiltrate into perivascular space of parenchyma

demonstrated larger vascular cellular infiltrates (Fig 6) These were often but not always associated with a more widespread and extensive leptomeningeal lymphocytic infiltration and extension of lymphocytes into the perivascular paces of the brain and spinal cord The latter could not be differentiated from a meningitis of a viral or chronic nature (Fig 7)

These changes were generally found more frequently within the leptomeningeal vessels of the brain than of the spinal cord In some cases similar changes were present within the choroid plexuses

These leptomeningeal vascular changes were not encountered until 2 weeks following the operative procedures Thereafter changes of varying severity were found in both groups as indicated in the Table As the interval between instillation of radiogold and autopsy become longer the cellular infiltrates were noted

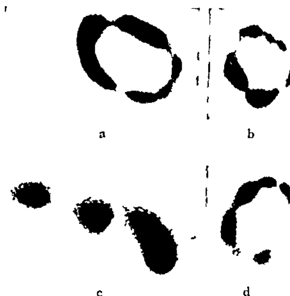


Fig 4 Autoradiograms of thin sections of the spinal cord of a dog sacrificed 2 days after intraventricular instillation of 5 mCi of ^{198}Au cervical cord (a) thoracic cord (b) cauda equina (c) and lumbar cord (d) There are hot and cold areas at various points around the circumference of the cord and relatively high activity along nerve roots in the cauda equina

the radiogold Sections of the spinal cord showed a similar distribution (Fig 4) Nerve root sheaths tended to retain a slightly higher concentration of the radio active material than the leptomeningeal surfaces of the spinal cord

In some dogs, the needle tract extended through the floor of the lateral ven tricle and into the basilar cisterns Comparison of the distribution of radioac tivity as determined by external counts, showed no significant qualitative or quantitative differences between those animals in which the tip of the catheter penetrated to the basilar cisterns and those where the instillation was into the lateral ventricle

There were no gross or microscopic changes ascribable to the gold in the cerebral or spinal cord parenchyma or nerve roots of any experimental or control animal except for the changes related to the surgical procedure

Microscopic changes were encountered, however, in blood vessels, primarily leptomeningeal veins, of the brain and spinal cord in both experimental and control animals Fourteen of the 19 dogs receiving radiogold and seven of the 12 control dogs showed these vascular alterations which varied in severity within and between groups

The most characteristic alteration was the focal accumulation of histiocytes, lymphocytes, and less commonly plasma cells eccentrically within and about the walls of leptomeningeal veins producing a picture of a nodular phlebitis (Fig 5)

In the less severely affected animals, involved veins were infrequently found and widely scattered At the other extreme, the most severely afflicted animals

fuse leptomeningeal infiltration seen in the dogs given radioactive gold Again, no changes were seen in the nervous tissue

In no case were gold particles definitely identified under the light microscope

Discussion

Some of the requisite data regarding the distribution and fate of radiogold has already been reported by Lewis (1953) and by Kerr and his colleagues (1954) In both reports the suggestion was made that the combination of internal and external sources of radiation might be advantageous Lewis demonstrated the rapid falloff in activity in the circulating cerebrospinal fluid following the intrathecal injection of the colloid indicating that this material soon adheres to the leptomeningeal surfaces Kerr et coll showed that a fairly even and circumferential distribution of the radioactive material could be obtained following introduction of the radionuclide via a cisternal puncture They employed barbotage (repeated withdrawal and reinjection of small aliquots of cerebrospinal fluid) for this purpose

Nonetheless both in animal and clinical investigations we have depended upon gravity to produce a relatively even distribution of the gold within the subarachnoid space This is because it has been found that simple barbotage of cerebrospinal fluid produces demyelination in the peripheral white matter of the spinal cord and medulla of cats (Bunge & Settlage 1957) This reaction has thus been avoided in the present study

The observations by Kerr et coll (1954) of peripheral necrosis in the spinal cord and of a significant proportion of the radioactivity in bone liver and spleen differ from the present study However the studies are not comparable due to these authors use of barbotage larger doses of radiogold lack of controls and shorter follow up times

The volume of the cerebrospinal fluid compartment in the dog is in the range of 20 ml The dose of 5 mCi of ^{198}Au thus produces a greater concentration of radioactivity in the cerebrospinal fluid than is obtained in the human where in the adult 15 mCi are introduced into an estimated volume of 130 ml (Riesselbach et coll 1962) Radiation doses delivered to the animals therefore exceed by a factor of two those to be expected in humans from a single injection of radiogold However it should be noted that in the regimen employed clinically patients receive three doses of radiogold at spaced intervals This is done in an attempt to equalize distribution of the radionuclide over the cerebrospinal axis Autoradiograms show that the most superficial layers of brain and spinal cord parenchyma receive varying dosages because of unequal distribution of the colloid that is there are hot and cold areas after a single dose Thus while the



Fig 7 From same animal as in fig 6 Diffuse infiltration of leptomeninges by lymphocytes and few acute inflammatory cells sparing cerebellar parenchyma

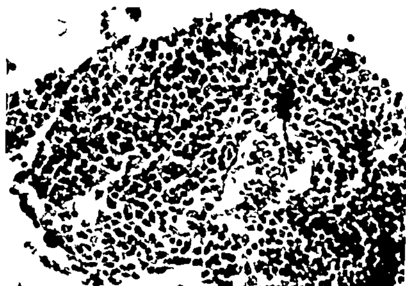


Fig 8 Cauda equina roots 18 months following cold gold Severe involvement of entire circumference of leptomeningeal vein by lymphocytes with rare plasma cells associated with prominent histiocytic mural cell hyperplasia hemosiderin pigment granules are present

to be larger and were encountered in greater numbers However, even in the *most severely affected animals with or without a picture resembling meningitis,* no parenchymal changes were identified

The vascular changes in the control animals represented the two extremes from no identifiable alterations to a very severe multifocal nodular phlebitis The changes were generally less severe than in the animals given radiogold (Fig 8) However, none of the control animals demonstrated the associated dif

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In Laboratoriumstudien an 19 Hunden wurde ^{198}Au intraventrikular injiziert und wahrend einer Beobachtungszeit von bis auf 18 Monaten wurde eine leptomeningeale vaskulare Reaktion aber keine Parenchymdegeneration demonstriert Ähnliche aber meistens weniger markierte Veranderungen wurden in 12 Hunden beobachtet die ein identisches Volumen von einem tatsachlich nicht radioaktiven kolloidalen Goldpraparat erhielten Die Tatsache dass das Parenchym des Gehirns und des Ruckenmarks nicht beschadigt wurde durfte zur Anwendung von intrathekalem radioaktivem Gold fur die klinische Behandlung von derartigen Neoplasmen wie Medulloblastom und Ependym anregen

RÉSUMÉ

Des études de laboratoire sur 19 chiens ayant subi une injection intraventriculaire de ^{198}Au et suivis pendant des periodes allant jusqu a 18 mois ont montré une reaction vasculaire de la leptoméninge mais pas de degénérescence parenchymateuse On a constate des lésions semblables mais en géneral moins marquees sur 12 chiens qui avaient reçu pour des raisons pratiques une injection identique d une preparation d or colloidal non radioactif L absence de lesion du parenchyme cerébral et medullaire a encourage les auteurs a utiliser l or radio-actif dans les espaces meninges pour le traitement clinique des tumeurs telles que le médullo-blastome et l ependymome

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total radiation dose is more than that given to the dogs, because of time dose relationships, the effect is less intense in the human

The only consistent histologic feature in the spinal cord of all animals examined is the lack of involvement of the spinal cord parenchyma This was particularly encouraging, since the rationale for utilizing intrathecal gold clinically is to give further irradiation to the leptomeningeal surfaces without exceeding the radiation tolerance of the spinal cord

The cause of the changes in the spinal leptomeninges is uncertain The leptomeningeal vascular reaction in both experimental and control dogs would suggest that if the phlebitis represents a response to the instillation of gold, it is the gold particle itself or the vehicle that is of primary importance rather than the radioactivity (The manufacturer states that vials of Aureotope contain small amounts of dextrose, gelatin, and sodium hydroxide as stabilizers The product also contains trace amounts of glyceryl monostearate, polyethylene glycol monostearate, silica, and silicone fluid) Operative trauma and its consequences may have played a role in producing the changes mentioned Also, one cannot exclude the possibility that a latent virus was activated or a micro organism was introduced during the operative procedure Regardless of the etiology, however, it would appear that the radioactivity may have accelerated the reaction or tended to make it more profound since the experimental animals were more consistently and severely affected However, the number of observations is insufficient to allow a definite conclusion on those points

These experimental results, notably the lack of changes in the parenchyma of the brain or spinal cord, have encouraged us to adopt this technique clinically Early results of this experience are reported elsewhere (D'ANGIO et coll) The regimen appears to be well tolerated by most of the patients treated to date

Acknowledgements

At the time of this work Dr Kieffer was a Scholar in Radiological Research of the James Picker Foundation The work was in part supported by USPHS Grants Nos CA 08832 CA 05190 and CA 08101 *The assistance given this study by Drs L French S Chou D Erickson J Ausman and M Loken* as well as Messrs T Nowak B Chanen S Bostrom and by Mrs K Gyorky is gratefully acknowledged

SUMMARY

Laboratory studies in 19 dogs given ^{198}Au intraventricularly and followed for periods up to 18 months have demonstrated a leptomeningeal vascular reaction but no parenchymatous degeneration Similar but generally less marked changes were found in 12 dogs given an identical volume of what was for practical purposes a non radioactive colloidal gold preparation The lack of damage to the brain and spinal cord parenchyma has encouraged the use of intrathecal radiogold in a clinical regimen for treatment of such neoplasms as the medulloblastoma and the ependymoma

study was to obtain a more definitive picture of the intracellular distribution of these agents by conducting autoradiography at the electron microscope level

Previous light and electron microscope studies (ref 26 27) have established that extensive cytologic damage is produced in spinal ganglion cultures exposed to 20 to 40 kR of roentgen rays Early findings (ref 24 25) from the present study indicated that AET chiefly in the MEG and GED forms, afforded significant radiation protection in this peripheral nervous tissue system, and that it was therefore appropriate to utilize this system for electron microscopic studies in an attempt to ascertain which cellular organelles are labeled and protected by these compounds The pre ent paper describes the results of these experiments, and correlates the findings with previous biochemical cell fractionation and ultrastructural studies carried out in other cellular systems

Materials and Methods Dorsal root ganglia excised from the cervical or lumbar regions of 18—20 day old rat fetuses were explanted onto reconstituted collagen coated coverslips in Maximow double coverslip assemblies and fed a complex culture medium twice weekly (for details see ref 7) In such preparations neuronal maturation and nerve fiber myelination occur in vitro providing after an 8—12 week period a highly organotypic model of peripheral nervous tissue (ref 7) Mature cultures were prepared for radiation protection studies by washing off the culture medium with balanced salt olution (pH 7 4) incubating the cultures for 20 min at ~30° C in a similar buffered solution containing 3 mM AET (or ^{35}S AET specific activity 0 1 mCi/mg) adjusted to pH 7 4 with 0 1 N NaOH according to the procedure of SCHWARTZ & SHAPIRO (1960) and placing the treated cultures covered with 0 1 ml of this same solution into plastic culture dishes (Prior experiments at higher and lower concentrations of AET showed either drug toxicity at higher concentrations or less efficacious radiation protection at lower concentrations — The ^{35}S AET was kindly supplied by Dr Bernard Shapiro Department of Radiology Albert Einstein Medical Center Philadelphia Pa) The assemblies were irradiated in air at ~30° C with 184 kV roentgen rays (30 mA 107 volt 0 28 mm Cu+0 50 mm Al filtration HVL=0 6 mm Cu TSD=15 cm) at a dose rate of 1 kR/min for a total delivered dose of 40 kR Directly following irradiation the cultures were washed and provided with fresh culture medium Control cultures were similarly treated and sham irradiated

Daily light observations were made on the living cultures, and at 1 4 8 and 14 day intervals representative specimens were fixed at ~3 C with Veronal acetate buffered 2 % OsO_4 (pH 7 4) containing 0 05 % Ca Cl and embedded in Epon 812 (ref 6) One micron sections were prepared from these embedded cultures and stained with a toluidine blue solution for viewing in the Zeiss Uni

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RADIATION PROTECTION IN MAMMALIAN SPINAL GANGLION CULTURES TREATED WITH AET DERIVATIVES

Light- and electron-microscopic autoradiographic studies

by

EDMUND B MASUROVSKY and RICHARD P BUNGE

The efficacy of AET (S [2 aminoethyl] thiuronium bromide hydrobromide), and its transguanylated derivatives MEG (2 mercaptoethylguanidine) and GED (bis[2 guanidoethyl]disulfide), as radiation protective agents has been demonstrated in a variety of biological systems over the past few decades (reviewed in ref 1) Though controversies have arisen concerning the exact mechanisms by which protection is conferred, it is generally recognized that one of the most important properties of good protective agents, such as MEG and GED is their ability to reach and interact with radiation sensitive sites within the target cells (ref 1 21) MAISIN and associates (1960, 1963) have demonstrated by light microscopic autoradiography that MEG as well as other AET derivatives penetrate and become distributed throughout the cytoplasm and nuclear regions of many mesodermal and entodermal cells in various stages of division and growth The resolution available by light microscopic autoradiography however, is not always adequate for a precise determination of which cytoplasmic or nuclear structures are labeled by such compounds One of the purposes of the present



Fig 1 AET treated dorsal root ganglion culture 8 days following 40 kR of roentgen irradiation This electron microgram illustrates neurons with normal appearing nucleolus (nl) nucleus (nuc) and cytoplasmic organelles [Golgi complex (g) mitochondria (m) ergastoplasm (eg)] which are closely invested by satellite cell processes (arrows) Most Schwann cells (sc) nuclear and cytoplasmic regions appear virtually unaltered morphologically as do the axons they invest ×10 100

versal microscope Thin (~400—900 Å) sections were obtained from the same tissue and stained with lead citrate (ref 29) and/or 50 % ethanolic uranyl acetate for examination in an RCA EMU 3 G electron microscope

The autoradiographic study was performed with ^{35}S AET labeled cultures fixed and embedded in Epon 812 immediately following treatment and roentgen irradiation Autoradiograms were prepared by applying a thin layer of dilute Ilford L 4 emulsion to 1-micron sections for light microscopy, or to thin sections carried on carbon reinforced filmed 200 mesh copper grids for electron microscopy, using the loop method described by CARO and VAN TUBERGEN (1962) Following exposure at 4° C, the autoradiograms were developed in Dektol (1 2), stained (ref 29), and examined as above In addition, assays were performed by liquid scintillation spectroscopy on the various solutions employed in the protection, fixation, and embedding procedures to determine which of these steps involved removal of certain AET derivatives

Observations

The damage occurring in acutely irradiated, unprotected dorsal root ganglion cultures has been described previously in detail (ref 26, 27) Abnormal neuronal changes generally develop relatively slowly during the first week following irradiation whereas certain satellite, Schwann, and connective tissue cells undergo acute degeneration within one day after exposure Cultures treated with AET solutions, and irradiated under identical conditions, appear not to be appreciably altered morphologically during the first week following irradiation The only definitive pathologic changes noted are in some capsule cells, and Schwann cells investing unmyelinated fibers These changes, which include diminution in number of ribosomes and focal membrane alterations, are less severe than those noted one day after irradiation of unprotected cultures During the 8 to 14 day post irradiation period, when severe radiation damage to neurons, satellite cells and Schwann cells (with or without associated myelin sheaths) is extensive in unprotected cultures, the AET treated cultures still retain many of their normal structural characteristics (compare Figs 1 and 2) This is especially striking at the electron microscopic level where cytoplasmic structures, such as mitochondria Golgi complexes, and ergastoplasm, appear within essentially normal morphologic limits in most neurons, this contrasts sharply with the severe damage to these organelle systems observed in unprotected irradiated cultures (Fig 2b) Nuclear and nucleolar ultrastructure also shows little deviation from the normal in AET protected cells in comparison to the variety of abnormal configurations which may be found in unprotected neurons (Fig 3, for details see ref 26) Most satellite cells also show little change, and continue to closely invest their respec-

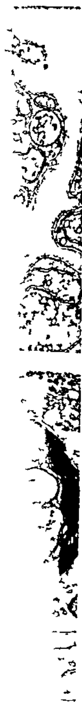


Fig. [illegible] This electro[illegible] nucleus [illegible] ergastop[illegible] Schwa[illegible] morpholo[illegible]

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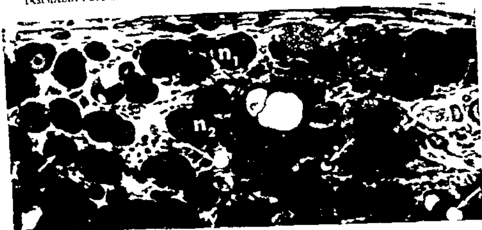
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a

erc

sc

b

Fig. Unprotected dorsal root ganglion culture 8 days following 40 kR of roentgen irradiation. a) Photomicrogram of a 1 micron section through the entire thickness of the ganglion explant. The top of the culture is at t. Several neurons display extensive signs of vacuolar

(cont. on opposite page)

tive neurons (compare Figs 1 and 2b) Certain connective tissue cells, and Schwann cells associated with unmyelinated axons, may display cytoplasmic and *nuclear membrane changes even after AET treatment (Fig 4a), but these af*fected cells represent only a minor proportion of the total population of such cells in these cultures Schwann cells investing myelinated axons, on the other hand, generally retain their normal appearance during this observation period, as does the contained myelin sheath (Fig 4a) This is in marked contrast to the degeneration of myelin, and associated *Schwann cells, in unprotected cultures* (Fig 4b, for details see ref 27)

Autoradiographic studies performed with serial 1 micron and thin sections reveal that ^{35}S labeled AET derivatives become bound to nuclear and cytoplasmic constituents in neurons, supporting cells, and capsular elements throughout the culture Since preliminary observations indicated that the distribution of these derivatives was essentially the same in control and irradiated cultures, the following illustrations and descriptions will be limited to the more important AET treated, irradiated cells

In *light microscopic autoradiograms,* silver grains marking ^{35}S binding sites appear over nuclei and nucleoli in neurons as well as in the other cells present in these cultures (Figs 5a and 5b) Some grains appear to be situated close to the nuclear envelope Numerous cytoplasmic structures are also overlaid by silver grains as are sites near the plasma membrane It is not possible to ascertain in such light microscopic preparations, however, which specific structures are labeled by these compounds

In *electron microscopic autoradiograms* silver grains appear as tortuously coiled, electron dense filaments overlying lighter ultrastructural features (Figs 5c, 6, and 7) In these preparations the nucleolus, as well as the nuclear matrix appears definitively labeled (Fig 5c) Sections taken perpendicular and at oblique angles to the nuclear envelope display silver grains contiguous with this structure (Fig 6) although the resolution of the system is not sufficient to state with absolute certainty that the envelope components themselves are labeled One has the impression, nevertheless, that regions in close proximity to the nuclear envelope, if not the envelope itself, contain binding sites for these compounds Within the

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Cont legend for Fig 2
degeneration (black arrows) Other neurons have notably eccentric nuclei (ni n) One neuron has a nucleus with an abnormal nucleolus (white arrow with asterisk) There are degenerating satellite cells and fascicular elements containing pyknotic and vacuolar areas (white arrows) ×750 b) The electron micrograph (lower view) shows a portion of a neuronal soma with loss of satellite cell investment (at black arrows) The cytoplasm contains numerous pleomorphic dense bodies and abnormally dilated endoplasmic reticulum cisternae (erc) some of which contain a moderately dense flocculent material (white arrows) An adjacent neuron contains an atypical whorl of neurofilaments (nf) Some of the Schwann cells (sc) investing unmyelinated axons are in the process of degeneration ×8 100

scu

a

my

b

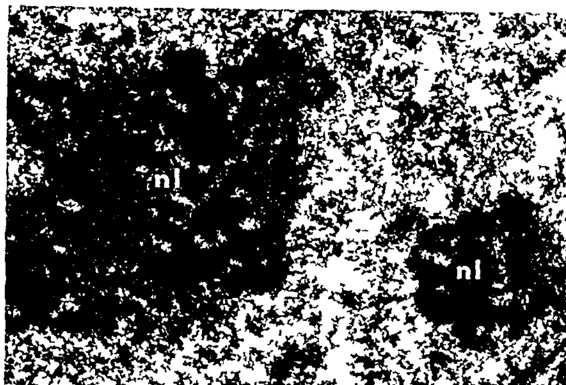


Fig 3 Electron micrograph of abnormal nucleolar configurations in an unprotected dorsal root ganglion neuron 8 days after 40 kR of roentgen irradiation Atypical dispersion and segregation of nucleolar (nl) components contrasts with the normal closely intermeshed skein like configuration illustrated in fig 1 × 25 500

cytoplasm mitochondria, ergastoplasm, and Golgi complex elements frequently display overlying silver grains (see Fig 6 and Table 1) Some dense bodies (i e lysosomes), and areas near the plasma membrane, also are overlaid with silver grains Whereas these observations are concerned primarily with neurons they apply equally to other cell types present in these cultures Within the nerve fascicles silver grains are often observed over axons, Schwann cells, and myelin sheaths (Fig 7) These findings are in accord with the radiation protection afforded these nerve fiber elements as well as the localization and protection ob-

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Fig 4 Electron micrograms of fascicles 8 days following 40 kR of roentgen irradiation a) AET treated Schwann cell (scu) investing several unmyelinated axons displays nuclear envelope and focal cytoplasmic degeneration a Schwann cell (scm) investing a single myelinated axon appears essentially normal as does the contained myelin sheath axons (asterisks) in both cells appear unaltered × 18 000 b) Unprotected Schwann cell cytoplasm around both the myelinated and unmyelinated axons (asterisks) showing signs of degeneration myelin (my) is breaking down about a large intact axon × 23 800



Fig 4a—b For legend see opposite page

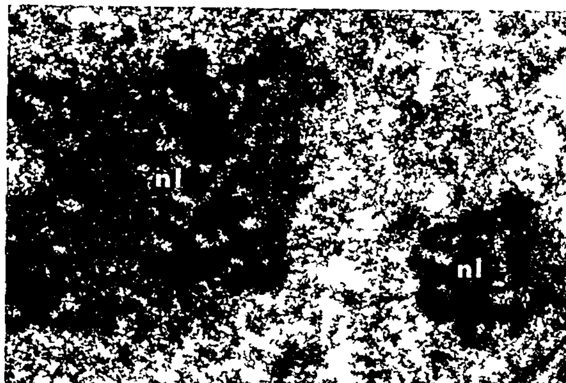


Fig 3 Electron micrograms of abnormal nucleolar configurations in an unprotected dorsal root ganglion neuron 8 days after 10 kR of roentgen irradiation Atypical dispersion and segregation of nucleolar (nl) components contrasts with the normal closely intermeshed skein like configuration illustrated in fig 1 × 25 500

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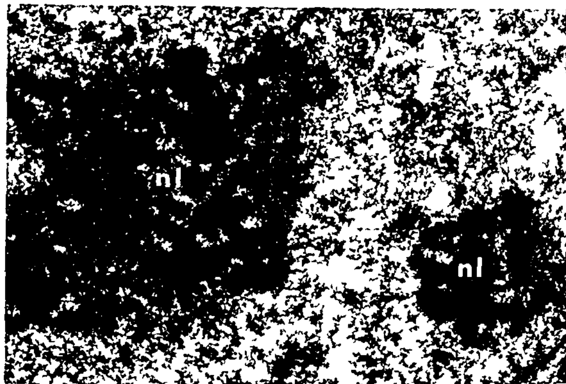


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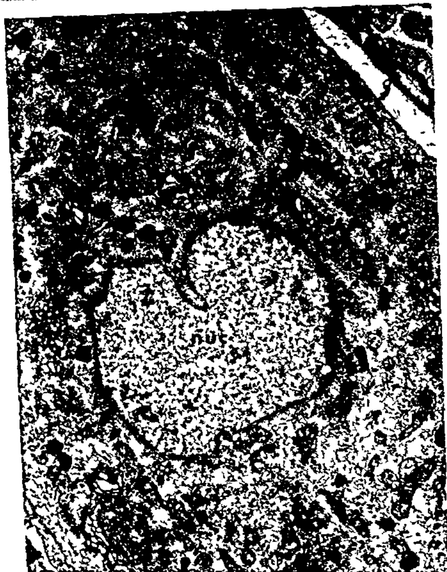


Fig. 6 Electron microscopic autoradiogram of an ^{35}S AET treated and roentgen irradiated neuron showing nuclear matrix (nuc) and possible juxtanuclear envelope (arrow) labeling In the cytoplasm mitochondria (m) Golgi complexes (g) and ergastoplasm (eg) are overlain by silver grains ×12 500

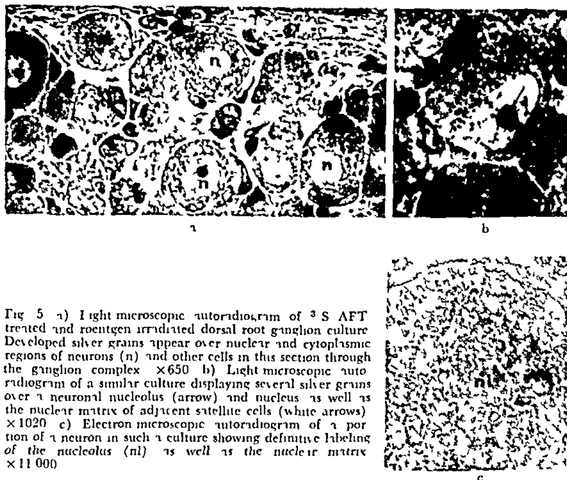


Fig. 5. a) Light microscopic autoradiogram of ^{35}S AET treated and roentgen irradiated dorsal root ganglion culture. Developed silver grains appear over nuclear and cytoplasmic regions of neurons (n) and other cells in this section through the ganglion complex. ×650. b) Light microscopic autoradiogram of a similar culture displaying several silver grains over a neuronal nucleolus (arrow) and nucleus as well as the nuclear matrix of adjacent satellite cells (white arrows). ×1020. c) Electron microscopic autoradiogram of a portion of a neuron in such a culture showing definitive labeling *of the nucleolus (nl) as well as the nuclear matrix*. ×11,000.

served in neuronal somas and supporting cells. Schwann cells associated with unmyelinated axons, and various connective tissue cells, also appear to contain these derivatives; the more radiosensitive members of their population, however, apparently do not benefit sufficiently from the protective compounds to survive this radiation dose.

Radioactive assay of ^{35}S AET samples, buffer rinse, and fixation, dehydration and embedding solutions (Table 2) indicates that over 50 % of the protective agents are taken up by the cells during the primary incubation and irradiation treatments and that, following the removal of free and loosely bound forms during the rinsing and fixation steps, relatively little (~0.3 %) is removed subsequently by the dehydration and embedding procedures. Thus it seems likely that no appreciable change had taken place in the initial binding site distribution of the strongly bound (e.g. protein bound) forms (ref. 1, 31) as a result of embedding the cultures in plastic (Epon 812).

Table 1

Silver grain counts of cytoplasmic regions in electron microscopic autoradiograms from roentgen irradiated rat dorsal root ganglion cells treated with ^{35}S AET derivatives

Cell region or organelle (excluding nucleus)	Total number of silver grains per cell region or organelle[a]	Percent of total silver grains counted
Mitochondria	130	29 0
Golgi complex	106	23 5
Ergastoplasm	96	22 0
Dense bodies	18	4 0
Plasma membrane vicinity[4]	44	10 0
Myelin sheath	24	5 5
Axon[6]	28	6 0
	446	100 0

1) A cell region or organelle was considered the probable (50 %) source of an ^{35}S beta emission giving rise to an exposed silver grain if >50 of it fell within a circle of radius $\approx$0 3 micron circumscribed about the midpoint of the exposed and developed silver grain (total error) Calculation criteria and procedures in ref 3 9 15 and personal communication (M SALPETER)

2) Total number of silver grains ascribed to a given cell region or organelle minus an average background grain count of ~5/μ

3) Dense bodies include a variety of subcellular structures which contain elements that have a noteable affinity for electron stains In this category are included lysosomes and lipofuscin granules

4) The plasma membrane and associated areas within a distance of <0 3 micron on either side for scattered radiation (see ref 3)

5 Myelin sheaths were considered labeled if over 50 % of the compact myelin sheath cross section was overlain by a silver grain

6 Axons were considered as labeled when >2/3 of a silver grain fell within the confines of the axolemma

corresponding to the protein-containing layers of the sheath (ref 7) however the interaction of GED with certain phospholipids is also possible (ref 17)

Although the nature of the chemical bonds formed between the protective agents and cell constituents has not been determined in the present study MEG is known to form mixed disulfides with protein thiol and disulfide groups as well as with radiation initiated intramolecular protein re arrangement complexes by disulfide interchange and radiation initiated free radical protein re arrangement reactions (ref 10)

Localization of AET derivatives in the nucleus and nucleolus of the neurons (and other cells in these cultures) is especially worthy of note since in the unprotected state these vital structures appear to be primary foci of radiation dam



Fig 7 Electron microscopic autoradiogram of a nerve fascicle in a similar culture (see fig 6) Labeling appears over axons (asterisks) Schwann cells (sc) and in relation to the myelin sheath (my) ×22 000

Discussion

The present study, conducted at both the light and electron microscopic levels, has shown that AET treatment prior to, and during roentgen irradiation affords significant cytologic protection to many of the cells comprising the rat dorsal root ganglion in culture Light microscopic autoradiographic techniques indicated that ^{35}S AET derivatives were widely distributed in nuclear and cytoplasmic regions of most cells These results are generally in accord with the classical light microscopic autoradiographic studies of MAISIN and associates (1950, 1963) in a variety of other mammalian tissues By extending our investigations to the electron microscopic level it has been possible to demonstrate, with greater certainty of organelle identification as well as with increased resolution, that AET derivatives may become bound to elements of the nucleus nucleolus Golgi complex, mitochondria, and ergastoplasm of neurons and other cells, in these cultures Other structures that appear to be labeled are dense bodies (i e lysosomes), juxtaplasmalemmal sites, and elements of the axoplasm and myelin sheaths of nerve fibers Labeling of myelin probably occurs chiefly in regions

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Table 2

Radioactive assay of ^{35}S AET derivatives in radioprotective buffer rinse fixation dehydration and embedding solutions

Sample[1]	Net counts/min[2]	^{35}S content of solution (% original AET solution)	^{35}S content of culture (% original AET solution retained in tissue)
Radioprotective ^{35}S AET solution *before treatment* of cultures	26 576	100 0	—
Radioprotective ^{35}S AET solution *after treatment* of cultures	11 428	43 0	57 0
Buffer rinse solutions following treatment and irradiation of cultures	2 923	11 0	46 0
Fixation solution	5 049	19 0	27 0
Dehydration and embedding solutions	80	0 3	26 7

1) Samples prepared immediately before liquid scintillation counting according to the procedure described in ref 5

2) Counts corrected for background efficiency and quenching total counts of 1 700 were obtained for a 5 error at the 96 % confidence level with samples of low ^{35}S content

age (ref 26) Recent biochemical and physicochemical studies (ref 17, 18, 19) have shown that certain diamino disulfide complexes (ref 18, 19) may be formed between GLD and DNA, as well as between GED and nucleohistones (ref 17), thus conferring protection upon this key macromolecular system against both indirect and direct effects of ionizing radiations RNA may also be protected by GED (ref 17)

Within the cytoplasm mitochondria, ergastoplasm, and the Golgi complex all severely damaged by this dose of roentgen irradiation in unprotected cells (ref 26), appear by morphologic criteria to be protected in AET treated cultures The frequency of protective agent labeling evidenced by these structures again appears to be correlated (in some measure) with the demonstrated radiation protection (see Table 1) These data, and those discussed above are in concordance with the statement of EIDJARN (1964) that ' the concentration of S containing protective agents in subcellular organelles or on structural surfaces is essential to cellular radiation protection

Additional electron microscopic evidence for AET localization and activity in these key cytoplasmic organelles may be found in the works of HUGON et coll (1964, 1966) They noted that a radioprotective dose of AET caused transitory alterations (i e dilatation) in mitochondria, ergastoplasmic cisternae, and Golgi

complex vesicles of certain mouse duodenal crypt cells Similar mitochondrial alterations were reported by FIRKET & LELIEVE (1966) in correlative electron microscopic and biochemical studies on the effects of radioprotective doses of a related thiolamine cystamine on various tissues in the rat

The observations pertaining to mitochondria are particularly significant in light of the findings by LEHNINGER and associates (ref 20 28) that radioprotective thiols and disulfides cause rapid swelling of mitochondria in suspension with the subsequent discharge or leakage of certain enzymes into the surrounding milieu They attributed these events primarily to thiol disulfide interchange between SH and SS groups in the membrane proteins of mitochondria and the SS or SH groups of the protective agents These observations appear to be in keeping with the enzyme release theory of BACQ & ALEXANDER (1951) and the revised general concept of chemical radiation protection in mammals recently advanced by BACQ (1965) According to that hypothesis the introduction of a radioprotective dose of thiol or disulfide into an organism results in the rapid intracellular binding (to proteins etc) of much of the protective agent(s) thereby disturbing the equilibrium between free and bound sulfhydryl compound (i e enzymes) within the cells leading to a transitory disruption in the regulation of redox potential and other key enzyme mediated processes Following the period of radiation protection these systems gradually re-establish their normal equilibrium Experimental as well as theoretical foundation for this hypothesis is provided (among others mentioned in ref 1) by the definitive work of ELDJARN & PIHL (1958, 1960) on mixed disulfide formation and the incisive works of DICKENS & SHAPIRO (1961) and SHAPIRO et coll (1963) on protein binding of protective thiolamines (especially AET derivatives)

Our results fit well within the framework of these and other (ref 4 32) biochemical and physicochemical investigations of the interactions of AET derivatives and related sulfhydryl protective agents with cellular constituents Since our data were obtained with radioprotective doses of freshly prepared buffered solutions of AET (chiefly MEG and GED) and the cultures were fixed at ice water temperature for autoradiographic study well within an hour of the time of administration and irradiation (when maximum protection was known to occur) drug dose metabolic and protection time artifacts should have been kept to a minimum

The noteworthy radiation protection afforded by this AET preparation in our spinal ganglion culture system suggests that it may be worth while to test the efficacy of topical application of the protective solution directly to the ganglion and environs in situ Such a stratagem could prove useful in radiotherapy regimes where protection of certain portions of the nervous system unavoidably exposed together with nearby radiation treatment areas is of crucial importance

Table 2

Radioactive assay of ^{35}S AET derivatives in radioprotective, buffer rinse, fixation, dehydration and embedding solutions

Sample[1]	Net counts/min[2]	^{35}S content of solution (% original AET solution)	^{35}S content of culture (% original AET solution retained in tissue)
Radioprotective ^{35}S AET solution *before treatment* of cultures	26 576	100.0	—
Radioprotective ^{35}S AET solution *after treatment* of cultures	11 428	43.0	57.0
Buffer rinse solutions following treatment and irradiation of cultures	2 923	11.0	46.0
Fixation solution	5 049	19.0	27.0
Dehydration and embedding solutions	80	0.3	26.7

1) Samples prepared immediately before liquid scintillation counting according to the procedure described in ref. 5.

2) Counts corrected for background, efficiency and quenching; total counts of 1 700 were obtained for a 5 % error at the 96 % confidence level with samples of low ^{35}S content.

age (ref. 26). Recent biochemical and physicochemical studies (ref. 17, 18, 19) have shown that certain diamino disulfide complexes (ref. 18, 19) may be formed between GED and DNA, as well as between GED and nucleohistones (ref. 17), thus conferring protection upon this key macromolecular system against both indirect and 'direct' effects of ionizing radiations. RNA may also be protected by GED (ref. 17).

Within the cytoplasm mitochondria, ergastoplasm, and the Golgi complex, all severely damaged by this dose of roentgen irradiation in unprotected cells (ref. 26), appear by morphologic criteria to be protected in AET treated cultures. The frequency of protective agent labeling evidenced by these structures again appears to be correlated (in some measure) with the demonstrated radiation protection (see Table 1). These data and those discussed above, are in concordance with the statement of ELDJARN (1964) that ... the concentration of S containing protective agents in subcellular organelles or on structural surfaces is essential ... to cellular radiation protection.

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SUMMARY

Studies of irradiation protection in mammalian spinal ganglion cultures revealed that transguanylated AET derivatives (MEG and GED) provide significant protection to essential cytoplasmic organelles (mitochondria Golgi complex ergastoplasm) and nuclear *structures in neurons as well as in other cells present in these cultures Light and electron* micros opic autoradiography using ^{35}S AET indicated widespread AET binding especially in relation to the aforementioned structures These observations in concert with previous studies by others point to an apparently close correlation between cellular radiation protection and the presence of AET derivatives in vital cytoplasmic and nuclear structures

ZUSAMMENFASSUNG

Beim Studium von mammalien Spinalganglienkulturen wurde festgestellt dass transguanylierte AET Derivate (MEG und GED) eine signifikante Strahlenschutzwirkung für die essentiellen cytoplasmischen Organellen (Mitochondrien Golgi Komplexe Ergastoplasmen) und nuklearen Strukturen der Neuronen und anderer Zellen in diesen Kulturen erbieten Bei Verwendung von ^{35}S AET wurden mittels Licht und Elektronenmikroskopie zahlreiche AET Bindungen mit den oben erwähnten Zellkomponenten observiert Diese Beobachtungen die in Übereinstimmung mit früheren von anderen Untersuchern publizierten Resultate sind deuten auf eine enge Korrelation zwischen Zellenstrahlenschutz und das Vorhandensein von AET Derivaten in den vitalen cytoplasmischen und nuklearen Strukturen

RÉSUMÉ

Des recherches sur la protection contre les radiations effectuées sur des cultures de ganglions spinaux de mammiferes ont montre que les dérivés transguanylés de l AET (MEG et *GED) fournissent une protection importante* aux organites cytoplasmiques essentiels (mitochondrie complexe de Golgi ergastoplasme) et aux structures nucleaires des neurones et des autres cellules presentes dans ces cultures L autoradiographie au moyen d AET marque par ^{35}S examinee en microscopie optique et electronique a montre des liaisons AET nombreuses en particulier en relation avec les structures mentionnees ci dessus Ces observations rapprochees des travaux faits par d autres auteurs montrent qu il y a apparemment une etroite correlation entre la radio protection cellulaire et la presence de dérivés AET dans *les structures* cytoplasmiques et nucléaires vitales

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RÉSUMÉ

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AUS DER RADIOISOTOPEN ABTEILUNG (PROF F MUNDINGER) DER NEUROCHIRURGISCHEN UNIVERSITATSKLINIK (PROF T RIECHERT) FREIBURG IM BREISGAU, DEUTSCHLAND

DIE INTRASELLARE PROTRAHIERTE LANGZEITBESTRAHLUNG VON HYPOPHYSENADENOMEN MITTELS STEREOTAKTISCHER IMPLANTATION VON IRIDIUM 192

von

F Mundinger

Mit der intrasellaren Permanent Implantation von Radioisotopen bei Hypophysenadenomen konnten die Therapieergebnisse signifikant verbessert werden (Mundinger 1961 1965 Riechert & Mundinger 1956 1957 Talairach u Mitarb 1956 1963 Notter 1959 u v mehr) Wir fuhren sie seit 1953 durch Die Implantation der Strahler erfolgt mit dem von Riechert gemeinsam mit mir konstruierten stereotaktischen Zielgerat (Riechert & Mundinger 1956 1959) Fur den transnasalen transsphenoidalen Zugang benutzen wir ein eigens hierfur entwickeltes Bohr und Implantationsinstrumentarium (Abb 1) mit Kanulenhalterung und Adaptionsteilen an unser stereotaktisches Gerat (Hersteller des Gerates Firma F L Fischer Fabrik fur Krankenhausbedarf, Freiburg i Br)

Liegt bereits eine suprasellare Expansion des Adenoms mit Chiasmasyndrom vor entfernen wir transkraniell (nach Dandy) oder transmaxillar transsphenoidal (nach Hamberger) zur Entlastung des Chiasma die suprasellare Tumorportion In einem zweiten Eingriff wird das Radioisotop intrasellar implantiert Bei allen

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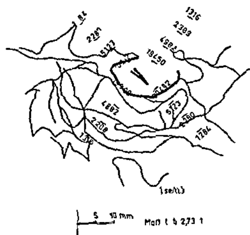


Abb 2 Isodosenzeichnung der stereotaktischen ^{192}Ir-Permanentimplantation in ein chromophobes Hypophysenadenom Gesamtaktivität 0 47 mCi

tion von ^{192}Ir-Drahten auch zur protrahierten Langzeitbestrahlung von Hypophysenadenomen eingeführt Der Zeitraum der Nachbeobachtung erscheint uns lange genug um die Nachuntersuchungsbefunde auszuwerten

Das ^{192}Ir hat eine Halbwertszeit von 74,3 Tagen Seine energetisch wichtigste Gammastrahlung ist 0 61 MeV seine Dosiskonstante 5 5 Die Iridium-Drahte mit einem Durchmesser von 0 3 mm und mit wechselnder Lange werden in das Tumorzentrum eingelegt (Abb 2) Die Aktivitat wird so berechnet daß auf der Isodosenlinie, die mit der Tumoroberflache korrespondiert, uber einen Zeitraum von 203 Tagen (2 75 fache Halbwertszeit) 20 000 rad akkumuliert werden Entsprechend hohere Dosen gelangen im Bereich des Tumors zur Absorption (Abb 3) Der Chiasmabereich soll dabei nicht mehr als 5 500 rad erhalten Abhangig vom Durchmesser der Tumoren variierte die implantierte Gesamtaktivitat verteilt auf ein oder mehrere kleine Drahtstucke zwischen 0 43 und 3 58 mCi Im letztgenannten Falle hatte das Adenom einen Durchmesser von 35 mm Die Patienten konnten in allen Fallen wenige Tage nach dem Eingriff nach Hause entlassen werden Besondere Strahlenschutzmaßnahmen waren nicht erforderlich

Mit dieser Dosierung haben wir uber die nahezu 7jahrige Nachbeobachtungszeit in keinem Falle eine Strahlenschadigung des Chiasma *oder der perisellaren* Strukturen beobachtet Auch ist in keinem Falle bisher ein Tumorrezidiv aufgetreten Nur bei *einem Patienten* trat vorubergehend eine Reduktion des Visus auf wahrscheinlich durch eine kleine intrasellare Blutung als Folge der Punktion verursacht Andere Komplikationen oder eine Operationsmortalitat fehlen Eine Patientin mit eosinophilem Adenom und schwerem *Diabetes mellitus* ist spater an einer hamatogenen Superinfektion bei Spritzenabszeß verstorben Nach der

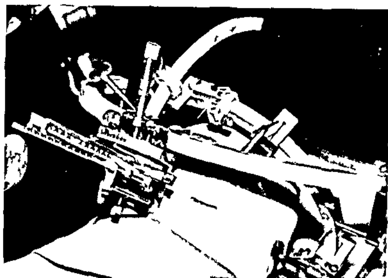


Abb 1 Operationssituation während der transnasalen stereotaktischen intrasellären Iridium 192 Implantation Die Bohrerführung steckt im Nasenlumen und ist an der Sondenhalterung des stereotaktischen Gerätes fixiert Die Implantationskanüle ist intrasellär eingeführt

übrigen Fällen legen wir primär stereotaktisch das Radioisotop ein Die Indikationsstellung und spezielle stereotaktische Implantationstechnik sowie Dosimetrie ist an anderer Stelle ausführlich beschrieben (MUNDINGER & RIECHERT 1967)

*Ausschließlich unserer zahlreichen Hypophysektomien und Instillationsbe*handlungen cystischer Kraniopharyngiome mit Radioisotopen haben wir in früheren Jahren bei 131 Hypophysenadenomen Radio-Phosphor in kleinen Kapseln und insbesondere als makromolekulare Suspension das Radio Gold an kleinste Graphitplättchen adsorbiert implantiert, denn unsere Ergebnisse mit Radio Gold Seeds brachten bei größeren Adenomen kein befriedigendes Resultat Die Langzeitergebnisse dieser Serien sind an anderer Stelle mitgeteilt (MUNDINGER 1961, 1965, MUNDINGER & RIECHERT 1967) Manchmal bereitete die Applikation der Radio Gold Suspension Schwierigkeiten, wodurch die Dosisabgabe ungenügend war Außerdem traten in 11,5 % der Fälle Strahlenfrüh und Spätschädigungen und Cystenbildungen infolge der relativ schnellen Dosisakkumulation des ^{198}Au auf (MUNDINGER 1965) Dies veranlaßte uns, trotz der sonst guten Ergebnisse nach einem anderen Strahler zu suchen Hierbei konnten wir *auf die Erfahrungen zurückgreifen, die wir seit 1957 mit der Permanentspickung* von ^{182}Ta und ^{192}Ir Drahtstückchen in langsam wachsende Hirntumoren (Astrocytome, Oligodendrogliome etc) gesammelt haben (MUNDINGER 1958, 1963, 1966) Deshalb haben wir ab April 1962 die intraselläre Permanentimplanta

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Abb 9 Isodosenzeichnung der stereotaktischen ^{19}Ir Permanentimplantation in ein chromophobes Hypophysenadenom Gesamtaktivitat 0 47 mCi

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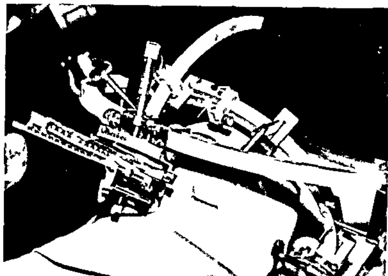


Abb. 1. Operationssituation während der transnasalen stereotaktischen intrasellären Iridium-192-Implantation. Die Bohrerführung steckt im Nasenlumen und ist an der Sondenhalterung des stereotaktischen Gerätes fixiert. Die Implantationskanüle ist intrasellär eingeführt.

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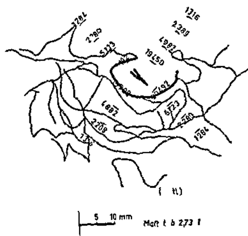


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tion von ^{19}Ir Drahten auch zur protrahierten Langzeitbestrahlung von Hypophysenadenomen eingefuhrt Der Zeitraum der Nachbeobachtung erscheint uns lange genug um die Nachuntersuchungsbefunde auszuwerten

Das ^{19}Ir hat eine Halbwertszeit von 74 3 Tagen Seine energetisch wichtigste Gammastrahlung ist 0 61 MeV, seine Dosiskonstante 5 5 Die Iridium Drahte mit einem Durchmesser von 0 3 mm und mit wechselnder Lange werden in das Tumorzentrum eingelegt (Abb 2) Die Aktivitat wird so berechnet daß auf der Isodosenlinie, die mit der Tumoroberflache korrespondiert uber einen Zeitraum von 205 Tagen (2 75 fache Halbwertszeit) 20 000 rad akkumuliert werden Entsprechend hohere Dosen gelangen im Bereich des Tumors zur Absorption (Abb 3) Der Chiasmabereich soll dabei nicht mehr als 5 500 rad erhalten Abhangig vom Durchmesser der Tumoren varierte die implantierte Gesamtaktivitat verteilt auf ein oder mehrere kleine Drahtstucke zwischen 0 43 und 3,58 mCi Im letztgenannten Falle hatte das Adenom einen Durchmesser von 35 mm Die Patienten konnten in allen Fallen wenige Tage nach dem Eingriff nach Hause entlassen werden Besondere Strahlenschutzmaßnahmen waren nicht erforderlich

Mit dieser Dosierung haben wir uber die nahezu 7jahrige Nachbeobachtungszeit in keinem Falle eine Strahlenschadigung des Chiasma oder der parasellaren Strukturen beobachtet Auch ist in keinem Falle bisher ein Tumorrezidiv aufgetreten Nur bei einem Patienten trat vorubergehend eine Reduktion des Visus auf wahrscheinlich durch eine kleine intraselläre Blutung als Folge der Punktion verursacht Andere Komplikationen oder eine Operationsmortalitat fehlen Eine Patientin mit eosinophilem Adenom und schwerem Diabetes mellitus ist spater an einer hamatogenen Superinfektion bei Spritzenabszeß verstorben Nach der

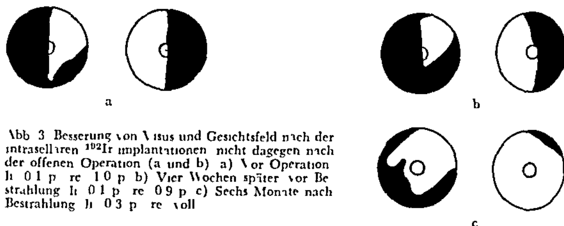


Abb. 3. Besserung von Visus und Gesichtsfeld nach der intrasellären ^{192}Ir-Implantationen, nicht dagegen nach der offenen Operation (a und b). a) Vor Operation: li. 0,1 p., re. 1,0 p. b) Vier Wochen später vor Bestrahlung: li. 0,1 p., re. 0,9 p. c) Sechs Monate nach Bestrahlung: li. 0,3 p., re. voll.

vierwöchigen Dosisakkumulation des ^{192}Ir war das Adenom bereits zu cirka 70 % zerstört, wie die Autopsie ergab. Alle übrigen Patienten sind am Leben.

Zum Zeitpunkt der Auswertung der Nachuntersuchungsergebnisse der 50 Patienten betrug die mittlere Nachbeobachtungszeit nach der Iridium-Implantation 2,26 ± 1,61 Jahre. Die Tabelle 1 zeigt die Änderung des Visus und Gesichtsfeldes nach der intrasellären ^{192}Ir-Implantation. Nur bei 2 bzw. 3 % der Augen sind im weiteren Verlauf Visus und Gesichtsfeld noch weiter zurückgegangen. Diese Patienten hatten bereits vor der Implantation einen defekten Sehstatus und eine Opticus-Atrophie. Bei 97 bzw. 98 % der Augen hat der Bestrahlungseingriff über die Nachbeobachtungsperiode zu einer Renormalisierung oder Besserung geführt oder der Augenstatus ist stationär geblieben. In keinem Fall war eine Rezidivoperation erforderlich.

Die Besserung oder Renormalisierung tritt gewöhnlich erst nach Wochen und Monaten auf, erklärt durch die langsame Schrumpfung des Tumors und dadurch Druckentlastung des Chiasma. In einigen Fällen wurde die bitemporale Quadranten- oder Hemianopsie renormalisiert, der reduzierte Visus auf normale Sehschärfe angehoben, und bei allen vier Fällen mit einer Abduzens- bzw. Occulomotoriusparese sind die Augenmuskellähmungen völlig zurückgegangen.

Tabelle 2 zeigt die Änderung der gonadotropen Funktionsstörungen nach dem intrasellaren Bestrahlungseingriff. 56 % der Frauen und 63 % der Männer mit chromophoben Adenomen, sowie 61 % der Frauen mit eosinophilen Adenomen hatten Ausfälle der gonadotropen Funktionen. Eine Besserung ist nur dann zu erwarten, wenn diese nicht länger als rund 3 Jahre vor dem Eingriff bestanden haben.

Die somatotrope Hyperfunktion der eosinophilen Adenome läßt sich in Übereinstimmung mit den Laborbefunden durch den Bestrahlungseingriff mit Iridium sehr gut beeinflussen. In allen Fällen war die Akromegalie zum Stillstand ge-

Table 1

Augenstatus bei Hypophysenadenomen nach stereotaktischer intrasellarer Implantation von ^{192}Ir (n = 50) Die Auswertung erfolgte nach Einzelaugen

Objektiver Befund	Visus		Gesichtsfeld	
Gebessert oder renormalisiert	24	97	53	98
Unverändert normal	56		29	
Unverändert defekt	17		16	
Verschlechtert	3		2	

Table 2

Änderung der gonadotropen Funktionsstörungen bei Hypophysenadenomen nach intrasellarer Implantation von ^{192}Ir (n = 50)

	Frauen		Männer	
	Besserung Renormalisierung	Präoperative Dauer der Störung	Besserung Renormalisierung	Präoperative Dauer der Störung
Chromophobe Adenome	45	<5 Jahre	33	<2 Jahre
Eosinophile Adenome	33	<1 Jahr	—	—

Table 3

Arbeitsfähigkeit nach intrasellarer Implantation von ^{192}Ir in Hypophysenadenomen (n = 50)

	Arbeitsfähigkeit			
	Voll	Teilweise	Fehlt	
Chromophobes Adenom	55	20	25 (13	altersbedingt im Ruhestand)
Eosinophiles Adenom	66	33		

kommen, was sich auch durch die Normalisierung des somatotropen Hormonspiegels objektivieren ließ. Bei 25 % der chromophoben Adenome war praeoperativ wegen der sekundären Nebennierenrindeninsuffizienz eine Substitutionsbehandlung erforderlich. Nach der Implantation wurde vorübergehend bei 21 % und auf die Dauer nur bei 8 % der Fälle Prednison verabfolgt. Somit hat sich nach der Zerstörung des Tumors das zur Peripherie verdrängte funktionell

druckgeschädigte Hypophysengewebe bei zwei Drittel dieser Fälle erholt. Im Gegensatz zur perkutanen externen Strahlentherapie schont offenbar die interstitielle Implantation infolge des steilen Dosisabfalles das nach dem Rand verdrängte Hypophysengewebe mit seiner höheren Strahlenresistenz. Eine möglichst intakte Hypophysenvorderlappenfunktion ist jedoch für die Wiederherstellung der Arbeitsfähigkeit von entscheidender Bedeutung (Tabelle 3).

Die Tabelle zeigt nach Abzug der altersbedingt in den Ruhestand getretenen Patienten mit chromophoben Adenomen nur 12 % nicht arbeitsfähige. Die Wiedereingliederung in den Arbeitsprozeß war bei diesen Patienten wegen ihrer Augenstörungen, endokrinen Ausfällen und subjektiven Beschwerden nicht mehr möglich. Alle Kranken mit eosinophilen Adenomen wurden nach der Iridium-Implantation entweder voll oder teilweise wieder arbeitsfähig. Keiner dieser Patienten blieb voll invalide.

Bei der Zusammenstellung der Befunde waren uns Frau Dr. Drewes und Herr Dr. Rayas behilflich, denen wir an dieser Stelle sehr danken. Die endokrinen Untersuchungen wurden in der Medizinischen Universitäts-Klinik Freiburg von Herrn Priv.-Dozent Dr. Reinert und Herrn Dr. Burmeister, die ophthalmologischen Befunde in der Universitäts-Augenklinik (Direktor: Prof. Dr. Mackensen) erhoben. Für die Überlassung der Befunde sprechen wir ebenfalls unseren Dank aus.

ZUSAMMENFASSUNG

Es wird über die Nachbeobachtungsergebnisse der stereotaktischen intrasellären Permanent-Implantation von Iridium 192 bei 50 Patienten mit chromophoben und eosinophilen Hypophysenadenomen berichtet. Diese Form der protrahierten Langzeitbestrahlung zeigt aufgrund der Nachbeobachtung bis zu 5,8 Jahren eine signifikante Überlegenheit gegenüber den früher mitgeteilten 131 Fällen mit der intrasellären Radio-Phosphor- und Radio-Gold-Implantation. Ausser einem Patienten sind alle am Leben. Klinische oder endokrine Zeichen eines Rezidivs sind nicht zu beobachten.

SUMMARY

The results of treatment by permanent stereotaxic intrasellar implantation of ^{192}Ir in 50 patients with chromophobe and eosinophil adenomas are reported. It could be ascertained *on the basis of follow-up periods of up to 5.8 years that this type of protracted irradiation* was significantly superior as compared with the intrasellar implantations of radiophosphor and radiogold in the 131 cases earlier reported upon. All the patients except one are alive and no clinical or endocrine signs of recurrence have been observed.

RÉSUMÉ

L'auteur présente les résultats éloignés de l'implantation permanente stéréotaxique intrasellaire d'iridium 192 chez 50 malades atteints d'adénome hypophysaire chromophobe et éosinophiles. *Cette observation prolongée jusqu'à 5,8 ans montre que cette forme d'irradiation de longue durée est supérieure à celle qui était réalisée par l'implantation intra-*

sellair de phosphore et d or radioactifs dont 131 cas avaient été publiés precédemment Tous les malades sauf un sont en vie et il n y a ni signe clinique ni signe endocrinien de récidive

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ROUND TABLE CONFERENCE
ON
GLIOBLASTOMA MULTIFORME

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INTRODUCTION

Vous savez que depuis 20 ans fonctionne à la Pitié un tandem qui s'appelle David—Fischgold, toutes les fois qu'on fait un progrès dans le diagnostic, David, et il a tout à fait raison parce que c'est son rôle, me dit à l'oreille « c'est bien ça, mais la maladie reste la même, et chirurgien, la question est de savoir si je fais un progrès avec vos connaissances diagnostiques, parce que si mon malade ne va pas bénéficier de vos connaissances diagnostiques, je ne dis pas que votre effort est sans intérêt, mais je dis que notre effort envers le malade s'arrête à mi chemin » Si ceci est une idée générale de David, dont il a réussi à m'imprégner et à me convaincre pendant nos 20 ans de collaboration fraternelle, ceci est particulièrement vrai pour les glioblastomes, parce que les glioblastomes, David qui n'aime pas se tromper avec des pseudostatistiques, David qui sait qu'un malade qui disparaît en matière de cancérologie, est un malade mort et non un malade ingrat qui ne se fait pas connaître, David me dit « nous sommes toujours en même point qu'au moment où toutes vos techniques n'étaient pas là » Et je crois que c'est pour ça que David, je le sais, il me l'a dit, a accepté avec le plus grand intérêt la proposition de notre ami, Martin Lindgren, de vous réunir ici, les gens intéressés par la radiothérapie, pour faire le point et pour savoir si premièrement vous avez, ou non, fait des progrès au cours des dernières années, et si vous n'avez pas fait de progrès le dire honnêtement et vous poser la question « Qu'est ce qu'il faut faire pour que ces malheureux, le médecin ne soit pas devant eux désarmé comme il l'est maintenant? » Si c'est le but de cette Table Ronde, je la vois avec le plus grand intérêt à l'intérieur de notre symposium

D Fischgold

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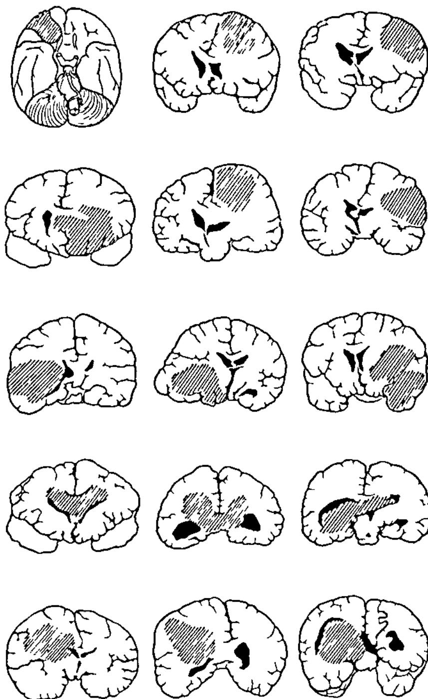
BIOLOGY AND MORPHOLOGY OF GLIOBLASTOMA MULTIFORME

by

K. J. Zülch

Of all the cerebral neoplasms glioblastoma multiforme is the one most like carcinomas of other organs: it occurs at the cancer age, grows at a rapid rate, infiltrates and destroys neighbouring tissues and forms metastases. The glioblastoma is, however, strictly localized to the system of the organ in which it arises, does not invade the mesodermal tissue (e.g. the dura) and produces metastases only in the subarachnoid space, that is in a part of its own organ. Where metastases from a glioblastoma multiforme occur in the extracranial organs, an incorrectly classified monstrocellular sarcoma is usually the true causal agent. However, the threat to life of the glioblastoma is comparable with that of most malignant growths. At least a fifth to a sixth of all *intracranial* tumours are glioblastomas, which thus form the most common cerebral neoplasms.

The first title under which this type of tumour appeared was the 'telangiectatic or haemorrhagic glioma' in Virchow's nomenclature. In the classification of Bailey & Cushing it occurred again under the heading 'spongioblastoma multiforme'; this was changed to 'glioblastoma multiforme' in order to avoid confusion with the (uni-) polar spongioblastoma. The latter is of course very benign. The term 'multiforme' is also macroscopically characteristic: a mixture of colours is evident in the brain section, the yellow of fatty infiltration, the



Preferential sites of glioblastomas

grey of necrosis and the red and brown of fresh and old haemorrhage A thick mantle of widely distributed vessels that gradually merge into the apparently normal tissue lie in the border zone of the glioblastoma Some glioblastomas are sharply demarcated from the healthy tissue The large vessels of the glioblastoma bleed easily as is evident from the colours described The marked oedema in the neighbourhood which may extend throughout the whole affected hemisphere is characteristic This increase in volume through oedema makes localization by pneumorraphy difficult it may also be impossible exactly to localize it if pathologic blood vessels are not contrast filled

The glioblastoma possesses another biologic characteristic that can be clearly demonstrated and which is particularly important for the neuroradiologist the predilection sites The most frequent sites are shown in the accompanying illustration The typical age incidence has been mentioned earlier glioblastomas seldom occur before the age of forty

There is also as in the other malignant neuro-ectodermal tumour the medulloblastoma an incidence twice as high in the male as in the female *in contrast* to the benign neurinoma and meningioma which predominate in women Histologically the glioblastoma may be classified according to whether spindle cells (fusiform) polymorph giant cells or multi nucleated cell varieties (multiform) or more rarely round cells (globuliform) predominate

The fundamental cell is however usually a small undifferentiated spindle cell with delicate protoplasmic processes which certainly has more cytoplasm than the equally malignant medulloblastoma The latter is very cellular and the cell processes can generally only be recognized after impregnation the number of mitoses in a medulloblastoma is also usually greater *More fundamental differences* exist however Both neoplasms are confined to a particular age the glioblastoma to the cancer age the medulloblastoma to childhood and adolescence The localization also separates the two tumours The glioblastoma occurs practically only in the supratentorial space in rare exceptions it may arise in the pons but never in the cerebellum The medulloblastoma is encountered only in the posterior fossa the pinealoblastoma (together with the sympathicoblastoma and retinoblastoma) should in any case be placed in the medulloblastoma group

Both histochemically and by the electron microscope there has to date been difficulty in recognizing and demonstrating the malignancy of brain tumours in particular analogous characteristics of both the medulloblastoma and glioblastoma groups cannot be established (ZÜLCH & WECHSLER 1968) Glial fibres are rarely demonstrable in the glioblastoma multiforme at ordinary microscopy although the electron microscope will reveal the finest glial fibrils and filaments Numerous mitoses may or may not be present The cell density is no reliable

indication of malignancy A comparison with the obviously more benign oligodendroglioma indicates that the glioblastoma is a less cellular and the medulloblastoma a more cellular tumour

The variegated appearance of the tissue in the glioblastoma will be explained if the stroma, and particularly the vascularization is investigated Six to eight entirely different types of new formed vascular systems, including fistulous or sinusoidal vessels may be recognized The walls are defectively constructed and the vessels are inclined to thrombosis so that the centre of the tissue tends quickly to necrose as rapid growth proceeds Small streak like and large massive areas become necrotic if the blood supply is not so suddenly interrupted as with thrombosis the tissue is only necrobiotic, i e it is destroyed by fatty infiltration or less frequently by liquefaction Small or even single large cysts may then *occasionally be formed This tendency to tissue degeneration is also a result of the* irregular formation of the vascular stroma

The blood supply of the glioblastoma is not only of interest to the morphologist but the vessels also play a leading role in the neuroradiologic diagnosis The numerous different types have been mentioned those with capillary glomeruli, cavernous like systems, adventitial proliferation, sinusoidal and fistulous vessels and other vascular systems A constant tendency has thus existed since VIRCHOW to designate a tumour with such a strong participation of mesoderm in its growth as a glio sarcoma, i e a tumour growing from two co ordinated germ layers

It is of importance to note (ZULCH 1939) that in practice the vascular mantle which is present in about 80 % of cases, makes the arteriographic diagnosis possible The newly formed vascular systems (e g corkscrew-like structures) as well as the arterio-venous shunts with early filling of the veins with arterial blood, are significant The red blood in the veins was noticed by the surgeon at an early stage (TONNIS 1938) The early veins in the angiogram are accepted as indications of a malignant tumour and today have a special significance Thus early veins have also been encountered in other tumours and in some infarcts (CRONQVIST 1968) they are in fact associated with a reactive hyperaemia (BIER 1902) The physiologist speaks of a luxury perfusion syndrome (LASSEN) It is understandable that the widely distributed vascular system of the cortical zone may function through dilatation of the arterioles capillaries and venules in the manner of an arterio-venous shunt similar to that occurring in the malignant and, chemically probably special tissue of such tumours

We do not know why this particular form of pathologic vascularization is not seen in the medulloblastoma for example which is just as malignant though markedly poor in vessels or in many metastases The hyperplastic or hypertrophic newly formed vessels may be accepted as indications of malignancy It

is interesting that they have been described at an early stage in osteosarcomas (e g by Dos Santos 1950) It is also unknown why they are sometimes absent in glioblastomas Again such pathologic vascularizations rarely occur in the highly malignant monstrocellular sarcoma They may be present in small foci in many malignant astrocytomas and oligodendrogliomas. This will be referred to in the biologic classification

The glioblastoma forms metastases only in the subarachnoid space either as small plaques on the ependyma (Spatz 1938 Hasenjager 1939) or as small rounded deposits on the spinal cord It should be mentioned that extra cranial metastases are usually derived from the monstrocellular sarcoma which of cour e bears con iderable similarity to the glioblastoma

There is thus no single definite morphologic characteristic criterion for the diagno is of glioblastoma e g the cell form It is much more an ensemble of all the variations of tissue structure that leads to the diagnosis Degenerative forms of cells and vessels parenchyma and stroma the rapid change in construction growth and degeneration of the tissue as well as the degeneration of vascular growth all characterize this particular tumour This combination of character istics easily di tinguishes the glioblastoma multiforme from metastases of disseminated extra cranial tumours undifferentiated carcinoma or sarcoma or the leuko-form of melanoma The multiform glioblastoma also occurs following the action of locally active (pellet) carcinogens it al o sometimes occurs after the ab orption of transplacentally active nitrosamines in the rat (Druckrey 1967 Ivankovic 1966) and in a few other animal species (Luginbuhl 1964)

The eparation of the multiform glioblastoma from the monstrocellular ar coma at microscopy is not biologically important because both have the same malignancy this depends on the inter cellular reticulin fibres and the monster cells Furthermore the monstrocellular sarcoma sometimes grows through the dura or completely infiltrates it Metastases may occur in the lungs The hi tologic differential diagnosis from the rapidly growing polymorphous oligodendroglioma is of considerable significance (Zulch 1959)

Confusion with a gliobla toma may easily arise when polymorphism is present to a high degree in the cells or some of the criteria—as for example small necroses and corresponding proliferation of the surrounding mesenchyma—occur in the ti ue of the oligodendroglioma Special impregnation will demonstrate however that these tumours actually stem from the oligodendroglial series and give a better prognosis than the glioblastoma Just as important is the differential di agnosis from polymorphous a trocytoma in which like the oligodendroglioma single characteristics from amongst those making up the ensemble of the glioblastoma occur (Zulch 1959 1962)

The biologic evaluation of the polymorphous astrocytoma and polymorphous

oligodendroglioma is the same Polymorphous spongioblastomas, plexus papil lomas, pinealomas, as well as gangliocytomas, with a higher grade of malignancy *than the normal forms of these tumours, occasionally occur* The pinealoma, because of its higher radiosensitivity, will therefore be mentioned in another paper (see p 92)

For the definition of sensitivity to ionizing radiation the criterion of biologic evaluation or malignancy of the individual groups is important and is dependent upon the rapidity of growth of the tumour tissue Double malignancy, i e the malignancy of the genuine tumour tissue and of the tumour as a neoplasm in the enclosed space of the skull, may therefore be distinguished by considering the 'clinical malignancy =the biologic (histologic) malignancy plus (1) volumen auctum, (2) mass movements with herniation, (3) action on the cerebro-spinal fluid pathway hydrocephalus, (4) action on arteries, and (5) action on vital *centers, such as the hypothalamus Here we should be concerned only with* the genuine malignancy of the tumour tissue The tumour as it grows will augment the volume, bring about mass movement, with eventual herniation into vital areas, and affect the cerebro-spinal fluid pathways with resultant hydrocephalus occlusus It will also act on the vessels, with the possibility of secondary infarction, and influence particularly sensitive centres in the hypothalamus, mid brain and medulla oblongata

The above conditions will modify the growth of genuine tumour tissue and produce the clinical malignancy Death may thus be caused by a quite benign tumour, e g a spongioblastoma of the aqueduct of relatively slow growth in the absence of a by pass operation for the cerebrospinal fluid The same applies to a large slow *growing meningioma in the frontal region* KERNOHAN (1949) made an attempt to express malignancy of neuro-epithelial tumours in four grades based upon the system of BRODERS (1926) This system has spread to some extent through the English speaking world because it seems precise and the clinician is always appreciative of attempts at precision *in the prognosis*

The present author has attempted to adapt this system satisfactorily to the biologic behaviour of brain tumours and to the desires of the neurosurgeon This seems to be necessary because not every type of tumour actually provides four grades of malignancy, these are usually limited to only two or occasionally three (ZULCH 1959 1962)

There are two grades of malignancy in the astrocytoma, oligodendroglioma spongioblastoma and the plexus papilloma as well as the neurinoma No histologic indication exists that the glioblastoma multiforme may develop from an astrocytoma or that the designations astrocytoma grade III or IV are appropriate However, a malignant form of astrocytoma that does not correspond to the high malignancy of the glioblastoma occurs in 5 % to 10 % of these growths

Table 1

UICC classification

1 *Nerve cells*
- Ganglioneuroma }
- Gangliocytoma } *
- Ganglioglioma }
- Ganglioneuroblastoma
- Malignant ganglioneuroma }
- Malignant gangliocytoma }
- Malignant ganglioglioma }
- Sympathogonioma
- Sympathicoblastoma }
- Neuroblastoma }

2 *Neuroepithelium*
- Ependymoma
  - epithelial
  - papillary
  - cellular
- Malignant ependymoma }
- Ependymoblastoma }
- Papilloma of choroid plexus }
- Plexus papilloma }
- Olfactory neuroepithelioma

3 *Eye*
- Medulloepithelioma of ciliary epithelium }
- Diktyoma }
- Neuroepithelioma }
- Retinoblastoma }
  - with true rosettes
  - without true rosettes

4 *Glia*
- Astrocytoma
  - fibrillary
  - protoplasmatic
  - gemistocytic
- Astrocytoma of the nose }
- Nasal glioma }
- Oligodendroglioma
- Multiform glioblastoma
- Polar spongioblastoma
- Medulloblastoma

5 *Peripheral and cranial nerves*
- Neurinoma }
- Neurilemmoma }
- Schwannoma }
- Neurofibroma**
- Malignant neurinoma }
- Malignant Schwannoma }
- Malignant neurilemmoma }

6 *Meninges*
- Meningioma
  - epithelioid }
  - meningotheliomatous }
  - endotheliomatous }
  - fibroblastic }
  - fibromatous }
  - psammomatous

7 *Vascular structures of central nervous system*
- Hemangioma of cerebellum
- Von Hippel Lindau's disease

8 *Paraganglia*
- Non chromaffin paraganglia includ }
- Carotid body tumor }
- Glomus caroticum tumor }
- Chemodectoma
  - adenomatoid
  - angiomatoid

9 *Pineal gland*
- Pinealoma

10 *Hypophysis*
- Chromophobe adenoma
  - diffuse
  - sinusoidal
  - papillary
- Oxyphil adenoma }
- Eosinophil adenoma }
  - papillary
- Basophil adenoma
- Craniopharyngioma }
- Adamantinoma of ductus craniopharyngeus }
- Chromophobe carcinoma

* Synonyms ** For sarcomas arising from neurofibromas *see* UICC pamphlet section VII

Table 2

Classification of brain tumours and their different degrees of malignancy

Degree of malignancy	Prognosis after radical removal	Tumours	
		Extracerebral	Intracerebral
Grade I benign	Cure or survival time of 5 and more years	Neurinomas Meningeomas Pituitary adenomas Craniopharyngeomas	Gangliocytomas (temporo basal) Ependymomas of the ventricles Plexus papillomas Spongioblastomas Angioblastomas (Lindau)
Grade II semi benign	Postoperative survival time 3—5 years	Pituitary adenomas polymorphous	Gangliocytomas of other location Ependymomas (cerebral) Astrocytomas isomorphous Oligodendrogliomas isomorphous Pinealomas anisomorphous
Grade III semi *malignant*	Postoperative survival time 2—3 years	Meningeomas polymitotic Neurinomas *polymitotic*	Gangliocytomas polymorphous *Ependymomas polymorphous* Plexus papillomas polymorphous Astrocytomas polymorphous Oligodendrogliomas polymorphous Pinealomas polymorphus
Grade IV malignant	Postoperative survival time 6—15 months	Sarcomas	Glioblastomas Medulloblastomas Primary sarcomas

The polar spongioblastoma which KERNOHAN includes as an astrocytoma grade I, is biologically entirely different from the usual cortical or subcortical astrocytoma of the supratentorial space The polar spongioblastoma (ZULCH 1959) may be distinguished histologically from the cerebral astrocytoma by its cells and architecture and particularly by the Rosenthal fibres and granular bodies (ZULCH & WECHSLER 1968)

RINGERTZ has devised a malignancy system of three grades similar to that of KERNOHAN Other forms of classification exist in the Portuguese and Spanish speaking countries particularly the HORTEGA (1932) system which POLAK

Table 3

Modified grading of tumours of the brain and related structures

Tumors	Grade I benign	Grade II semibenign	Grade III semimalignant	Grade IV malignant
Ga lioeytoma				
Isomorphous	+	+		
Poly morphous			+	
Ep dymom				
I omorphous	+	+		
Polymorphous			+	
Plex s papill ma				
I omo phous	+			
Poly mo phous			+	
A t ocyt m				
Isomorphous		+		
Polymorphous			+	
Ol god nd gl ma				
Isomorphous		+		
Poly morphous			+	
Gl obla t ma				+
Sp giobl st m				
Isomo phous	+			
P lymorphous			+	
Medull blastoma				–
P ne loma				
Isomorphou	+			
A somo phous		+		
Polymorph us			+	
N u i oma				
Am tot	+			
Poly m tot			+	
M g m				
Am t t ol gom totic	+			
P lymitot			–	
A g bl t ma (LI DAU)	+			
Sa ma				–
P tu ta y d ma				
Isomorphous	+			
Poly m phous		+		
C pha y g ma				

(1966) has recently re-outlined. Similar structural elements, as those upon which the most frequently applied system of BAILEY & CUSHING (1926) are based, are used. This classification, with modifications that have arisen from the works of PENFIELD (1931) and BERGSTRAND (1932), is employed by the present writer.

It must be recognized that the terminology is unfortunately not uniform which makes it difficult to compare statistics of treatment results. The International Union of Pathologic Societies has published a compromise system, which may prove helpful (UICC 1965). KERNOHAN has been a member of the nomenclature commission that concerned itself with this compromise. The International Symposium in Cologne 1964 on the classification of brain tumours (ZÜLCH & WOOLF 1964) discussed this schema and undertook its improvement. The schema of neuroepithelial tumours in the book of the UICC corresponds to that of BAILEY with our modifications. It does not entirely conform to our desires but will be adopted in future in order to facilitate the achievement of a uniform nomenclature (ZÜLCH & WECHSLER 1968).

The valuable advance provided by KERNOHAN's biologic grouping into four grades of malignancy must not be forgotten (ZÜLCH 1962, 1964). These four categories correspond to the traditional custom of designating a tumour benign, semi-benign, semimalignant or malignant.

An attempt has been made in the schema (Tables 2 and 3) to indicate the malignancy of intracranial tumours by adopting the classification of the UICC (Table 1). The concept of benign to malignant with intermediary stages is based on the average numeric result of postoperative survival. It was mentioned that for the real prognosis of a particular tumour the malignancy of growth must be assessed in conjunction with clinical factors, from these the true malignancy emerges and its establishment is the duty of the clinician and not of the morphologist (see p. 70).

The glioblastoma is placed in group IV together with the medulloblastoma and the sarcoma, and the remaining known epithelial and particularly important tumours lie in the corresponding groups (Tables 2 and 3).

This schema corresponds both to the experience of the clinician and the findings of the morphologist and satisfies the desire of the neurosurgeon for a relatively precise numerically expressed prognosis so far as is possible. Only with a uniform classification of cases in three groups of patients with either irradiated or operated tumours or combined treatment is it possible to produce an exact statistical comparison of different methods. This classification precisely describes the morphology of the tumour groups, their normal varieties and those occurring through regressive changes. The comparison of synonyms makes possible a corresponding transposition of the terminology of other classifications, as in the atlas of the Unio Internationalis Contra Cancrum. An international under-

tanding of the definition and terminology of brain tumours from the precise data of today is the prerequisite for all attempts to assess the value of methods of treatment of the glioblastoma Without this no discussion on treatment is complete

SUMMARY

The morphology and biology of the glioblastoma multiforme are presented The different classification systems are indicated and the difficulty of their appreciation and comparison because of the varying terminology is emphasized A new 4 stage grouping for the malignancy in which the various tumours occurring in the brain and spinal cord can be included is suggested

ZUSAMMENFASSUNG

Es wird eine Übersicht über die Morphologie und Biologie des Glioblastoma multiforme gegeben Die verschiedenen Klassifikationen werden besprochen und die Schwierigkeiten der Einordnung in eine feste Klasse bei der bestehenden Verwirrung in der Terminologie wird betont Eine neue Vierstufen Malignität wird vorgeschlagen in die die einzelnen an Hirn und Rückenmark vorkommenden Tumorarten eingeordnet werden können

RÉSUMÉ

L auteur décrit la morphologie et la biologie du glioblastome multiforme Il indique les différents systèmes de classification et souligne la difficulté de les juger et de les comparer en raison de la terminologie variable Il propose un nouveau classement en quatre grades de malignité dans lequel on peut faire entrer les différentes tumeurs du cerveau et de la moelle

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FROM THE ROENTGENDIAGNOSTIC DEPARTMENT (DIRECTOR PROF. OLLE OLSSON),
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ANGIOGRAPHY AND CEREBRAL BLOOD FLOW IN MALIGNANT GLIOMA

by

STEN CRONQVIST

A malignant glioma appears angiographically as a more or less expansive, vascular or avascular, lesion. Both forms may present diagnostic difficulties.

The degree of vascularity of a glioma may range from an abundance of irregular tortuous vessels to a single abnormal vein. Arteriovenous shunting is considered characteristic of a malignant glioma; it may be extensive and cause the immediate passage of contrast medium from arteries to enlarged and tortuous veins. The increased flow is then reflected in widening of the arteries feeding the neoplasm (Fig. 1a); when this occurs the angiographic findings are similar to those in arteriovenous malformations (Fig. 1b) and differentiation may indeed be difficult. A malignant glioma has been said to present no avascular tissue in between the abnormal vessels, while, in an arteriovenous malformation, normal brain tissue may usually be found between the widened vessels. This difference may be of some help in isolated cases but is generally of restricted value.

A vascular glioma may sometimes be difficult to differentiate also from a highly vascularized meningioma. It is generally held that arteriovenous shunts seldom occur with meningioma, but such shunting can occur (Fig. 2) as has also been pointed out by STATTIN. One of the characteristics of a malignant glioma may thus be found even in the benign meningioma. The differentiation is then



Fig 1 Angiography of a malignant glioma (a) and arteriovenous malformation (b) In both there is dilatation of the arteries feeding the lesion the configuration of the vessels within the respective lesions is almost indentical

generally based upon the fact that a meningioma may receive some of its blood supply from the external carotid artery However even a glioma infiltrating the dura may be mainly fed by the external carotid artery (Fig 3) Angiographic determination of the local circulation time i e the tumour circulation then most often affords an indication as to the nature of the process

Metastases like a glioma may possess an abundance of irregular vessels as well as arteriovenous shunts Displacement of surrounding vessels extending beyond the confines of the vascular lesion itself is often noted Such a discrepancy is due to the edema so often present in fast growing tumours and favours the diagnosis of metastases A fast growing glioma may however present identical changes

Abnormal filling of a local vein may be the only angiographic sign in poorly vascularized gliomas Such a vein may appear earlier or later than normal i e it may be seen already in the arterial phase as well as in the capillary or even in the late venous phase According to recent observations an early filling vein is a frequent finding in cerebrovascular lesions and has been noted both in arterial occlusion and intracerebral hematomas (Fig 4) Because of this, a cerebrovascular lesion has to be considered whenever such a vein occurs The possibility that the vein represents a micro-arteriovenous malformation should not be overlooked

One of the characteristics of a malignant glioma is the rapidity of growth It is not unusual for such a tumour to appear as only a slight expansivity at the first angiographic study At repeat angiography one or two weeks later marked progression may have occurred represented not only by an increased expansivity

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Fig 2 Frontal meningioma partially fed via the ophthalmic artery arteriovenous shunting



Fig 3 Malignant glioma infiltrating the dura feeding vessels mainly from the external carotid artery

but also by an abundance of pathologic vessels and arteriovenous shunts (Fig 5) Rapid growth is in fact so frequent as to be of differential diagnostic significance Repeat angiography after a short interval will most often provide a correct diagnosis in cases with early filling of a single vein An increase in the number of pathologic vessels may be expected in a malignant glioma In micro-arteriovenous malformations, the venous filling should remain unchanged Venous filling is known to be transitory in a cerebrovascular lesion, and thus if repeat angiography discloses the disappearance of an abnormal vein, the lesion may be considered as having been vascular

It is a well known fact that the various parts of a tumour may present entirely different pathologic appearances This is of importance in the roentgenologic determination of the nature of the growth and was well illustrated in a case in which angiography first revealed the presence of an avascular process in the temporal region, this at operation was found to be an astrocytoma The clinical condition did not however improve, and at repeat examination pathologic veins were found posterior to the operation area Further operation disclosed a malignant glioma in the region (Fig 6)

A completely avascular expansivity may be encountered in a variety of intracerebral lesions and the roentgenologic diagnosis of its nature may often prove difficult The use of radioactive isotopes as in gamma encephalography, would appear to be of definite value in the determination of the nature of a tumour in these cases Repeated studies should then be made after injection of the isotope

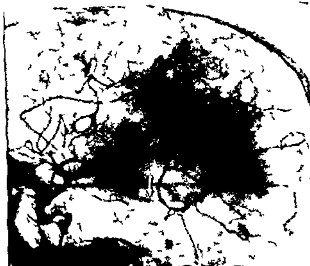


Fig 4 Early filling vein in the temporal region at angiography in a case of cerebrovascular disorder

since increase and decrease of the activity within a lesion seems to vary with the type The sequence is roughly as follows The time interval between the two studies varies with the isotope used In a meningioma marked activity is observed in a study performed shortly after the administration of the isotope and



a b

Fig 5 Fast growing malignant glioma a) Slight expansivity without pathologic vessels b) Angiography performed 14 days later Marked enlargement of the expansive process with abun of patholog c vessels

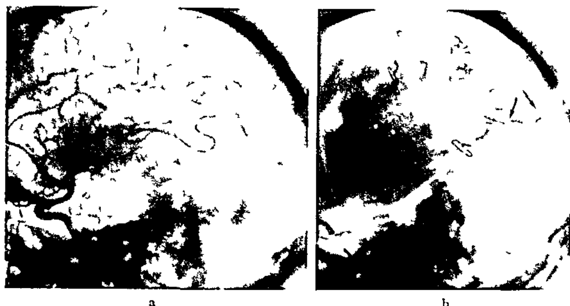


Fig 6 Vascular expansive lesion with upward displacement of the Sylvian vessels a) Deformed arteries in the posterior parietal region operation on temporal region revealed astrocytoma Arteriovenous shunts in posterior parietal region (arrows)

remains fairly unchanged in a later study A malignant glioma generally presents an increase in activity between the first and the second study, while intracerebral haemorrhage has a fairly high initial uptake which decreases at a repeat study It should be stressed that this development is a generalization and that variations occur in individual cases

In the last few years a new method has been developed for the determination of cerebral blood flow The isotope clearance method, as it is called, implies the use of the radioactive inert gas ^{133}Xe which dissolved in saline, is injected into the internal carotid artery The initial uptake and subsequent clearance of the isotope is measured with one or more extracranial scintillation detectors The clearance curve is assumed to consist of two mono exponential functions representing a fast and a slow type of flow The flow of these two components as well as the average flow, can be calculated from the curve in terms of ml 100 g min

A clearance curve in normal tissue presents a characteristic form After a sharp initial rise it reaches a point from which an almost linear fall in the initial part occurs (Fig 7) If the curve is obtained from an area covering the carotid siphon there is also a sharp rise that reaches a height which is far above the point from which the linear fall started This peak is caused by the rapid transit of the bolus of isotope when passing through the field of the detector

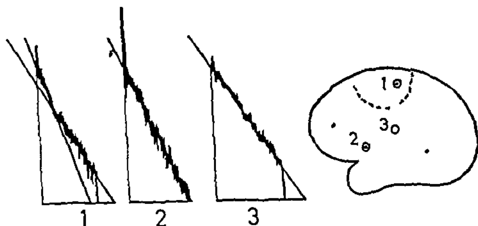


Fig 7 Regional cerebral blood flow measurem nts Semi logarithmic representation of the in tial parts of the clearance curves obtained s multaneously over different regions Three com ponents in the reg on marked (1) indicate not only a shunt peak but a second peak to suggest rapid regional flow (ti sue peak) Th re are two components in curve (2) with signs of rapid transportation of the isotope bolus (carotid or shunt peak) One component in the normal curve (3)

Whenever possibilities for such a rapid transportation through the field of a detector exi t such a peak may be seen that is to say it will probably be found in the presence of arteriovenous malformations or pathologic arteriovenous shunts

The clearance curve obtained over a malignant glioma presenting angiographic signs of pathologic vessels (arteriovenous shunting) has a form differing from that normally encountered There is an initial peak of the same kind as ob erved over the carotid siphon but in addition a second peak of longer dura tion occurs demonstrating the presence of an additional component in this part of the curve Thus in addition to the normal fast flow, there is one more component with a till faster flow This we have called a tissue peak The presence of such a peak indicates an increased flow (Fig 8)

It has earlier been demonstrated that a focal lesion within the brain exerts general effects upon the cerebral blood flow, both within the hemisphere af fected and on the contralateral side This also applies in cases of brain tumours in which a general decrease in the cerebral blood flow amounting to about 30 % of the normal fast flow has been ob erved

In a series of thirty six tumour cases the blood flow was determined in 4 to 8 regions imultaneously Local blood flow changes within the area corresponding to the tumour were also observed in most of the cases (twenty three) The flow in the tumour was found markedly to exceed the flow in the rest of the hemi-

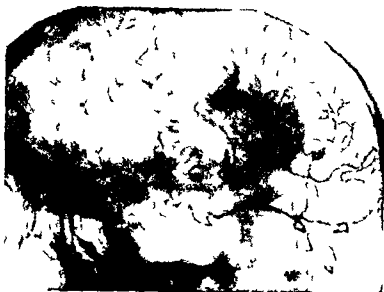


Fig 8 Angiogram from same case as in fig 7 Well defined malignant glioma with pathologic vessels and arteriovenous shunts in the region corresponding to (1) in fig 7

sphere, i e there was a relative hyperaemia When relating the flow values to the angiographic changes, the highest flow occurred over tumours with abnormal vessels and arteriovenous shunts No increase in flow was induced when only abnormal vessels were present Eight out of eleven avascular tumours had a flow well below that of the non malignant tissue, the remaining three cases had, however, a high tumour flow This is interesting since local hyperaemia could be demonstrated with the isotope clearance method, indicating the presence of arteriovenous shunts in cases that angiographically appeared completely avascular

In cerebrovascular lesions, relative hyperaemia as well as signs of locally increased transit time arteriovenous shunting, have been recorded There is ample experimental evidence that these changes are secondary to anoxia and acidosis within the lesion It is tempting to speculate about the presence of the same mechanism in neoplasms Anoxia may be expected to occur within a tumour and, due to pressure effects, also in the immediate surroundings of a tumour An early filling vein, in cerebral vascular lesions found to be related to a local relative hyperaemia may often in fact encircle a glioma, and there are strong reasons to believe that in some cases of new growths with local hyperaemia this is confined to the boundaries of the tumour

The fact that both tumours and cerebral vascular lesions may present similar or identical changes both in regard to blood flow and angiographic appearances,

this one must conclude that in every cases of possible malignancy the final diagnosis should be confirmed by biopsy before radiotherapy is instituted

SUMMARY

The difficulties of differential diagnosis in the roentgen examination of vascular and avascular malignant gliomas are discussed The value of angiography the determination of the cerebral blood flow and the use of gamma-encephalography are all considered

ZUSAMMENFASSUNG

Die Schwierigkeiten der Röntgendifferenzialdiagnose zwischen den gefässreichen und den gefässarmen malignen Gliomen werden besprochen Der Wert der Angiographie der Bestimmung der Gehirndurchblutung und der Gammaencephalographie werden diskutiert

RÉSUMÉ

L'auteur examine les difficultes du diagnostic differentiel radiologique des gliomes malins vasculaires et avasculaires Il etudie la valeur de l'angiographie de la mesure du debit sanguin cerebral et de la gamma encephalographie

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GAMMA-ENCEPHALOGRAPHIE

Possibilités et limitations dans le diagnostic de la présence et de l'extension des glioblastomes

par

THÉRÈSE PLANIOL

La présence d'un foyer radio-actif s'observe actuellement dans plus de 90 pour cent des cas de glioblastome. Pour fixer les idées voici les chiffres résultant de notre revue la plus récente. Sur 537 gamma-encéphalogrammes effectués chez des malades porteurs d'une telle tumeur, 503 ont été positifs dès le premier examen, dix sont devenus positifs au cours de la surveillance: 3 entre deux et quatre mois, 7 entre un et deux ans. Dans les 24 cas où le gamma-encéphalogramme négatif n'a pas été répété ultérieurement, les particularités suivantes furent relevées à l'examen macroscopique ou histologique: volumineux kyste associé à une faible masse de tissu plein (4 fois), astrocytome dégénéré comportant des plages de cellules différenciées (7 fois), caractère isomorphe du glioblastome avec apparition de signes de haute malignité (8 fois).

A côté de ces 537 cas 111 malades ont été examinés plusieurs mois après l'opération, soit par mesure de contrôle, soit parce que la recrudescence des signes cliniques laissait craindre la reprise du processus néoplasique. Cette reprise existait chez les 111 malades, ainsi que le prouvèrent l'évolution, les examens, les vérifications anatomiques. Le gamma-encéphalogramme fut négatif 4 fois et dans des cas de glioblastome isomorphes où il avait été négatif avant l'exérèse

Au total en ce qui concerne la mise en evidence de la tumeur il est probable que la gamma-encephalographie atteigne avec la proportion de 94 % ou 95 % la limite de ses possibilites Nous pensons avoir ameliore notre technique d examen dans les dernieres annees et nous avons utilise tous les composes marques disponibles Cependant sur nos 130 derniers cas depuis le debut de 1966 cinq sont negatifs et six ne sont devenus positifs que secondairement Il est fort possible qu intervienne ici en plus de la limite de sensibilite des detecteurs actuels l obstacle d ordre biologique que soulevent les astrocytomes benins ou peu malins (disons les grades I et II de la classification de Kernohan) qui pour la plupart ne sont guere plus permeables que le tissu cerebral sain aux composes radioactifs habituellement employes en gamma encephalographie

En fait, la mise en evidence d un foyer radioactif ne fait que reveler ou confirmer la presence d une lesion dont il reste a determiner les caracteres topographie exacte extension rapports avec les structures voisines vascularisation nature histologique La gamma encephalographie contribue a preciser certains d entre eux mais ne fournit aucune information sur d autres

Par la technique de comptage au contact du crane (gamma-contact) divers parametres peuvent etre apprecies quantitativement Deux nous ont des le debut paru essentiels pour orienter le diagnostic histopathologique le gradient de radioactivite a la peripherie du foyer et l evolution de l hyperactivite maximale de ce dernier en fonction du temps ecoule depuis l injection du compose marque Les criteres que nous avons etablis avec la SAI 131 peuvent etre transposes aux cas ou d autres traceurs sont utilises a condition de modifier convenablement les intervalles de temps entre les sessions de comptages Au « gamma contact » nous associons la scintigraphie (a laquelle nous affectons le terme de gamma planigraphie (compatible avec l emploi de detecteurs stationnaires aussi bien que conventionnels) Nous disposons ainsi d un ensemble de donnees visuelles numeriques et dynamiques necessaire pour approcher le diagnostic non suffisant pour le preciser totalement

Les principaux caracteres gamma encephalographiques qui conduisent au diagnostic de glioblastome (parce qu ils sont observes dans environ 70 % des cas de ces tumeurs) sont la delimitation tres floue qui marque la peripherie du foyer et l augmentation progressive de l hyperactivite relative au lieu d intensite maximale Ce qui empeche ces caracteres de prendre une valeur pathognomonique est la possibilite de les rencontrer dans d autres affections les accidents cerebro-vasculaires d abord plus rarement d autres neoformations

Les accidents vasculaires a type de ramollissements se traduisent parfois par des foyers radioactifs de meme type que ceux des glioblastomes Nous avons rencontre de tels foyers dans les ramollissements avec thrombose confirmee par l angiographie Cette hyperactivite lesionnelle semble beaucoup plus frequente

Tableau 1

Aspects macroscopiques et histologiques de 39 glioblastomes à foyer gamma encéphalographique atypique (sur un total de 430 cas vérifiés)

Nombre de cas	Gamma encéphalographie		Remarques			
	Anomalies du foyer	Diagnostic porté	Macroscopiques		Histologiques	
14	Précocité, intensité d'emblée élevée, limites nettes	Méningiome	Bien circonscrits	9	Type isomorphe	9
					À cellules fusiformes	3
					Caractère angioblastique	2
25	Retard d'apparition, limites nettes	Métastase	Bien circonscrits	13	Type hétéromorphe	21
			Kyste volumineux	6	Type isomorphe	4
					Avec nécrose +++	15

et plus intense avec le technetium qu'avec la serumalbumine radio iodée. Néanmoins l'aspect diffus de la zone hyperactive, son siège le plus souvent le long de la scissure sylvienne, et cortical, ajoutés aux arguments cliniques, réduisent le nombre d'erreurs possibles. Dans les cas les plus difficiles c'est la régression du foyer au cours de contrôles successifs qui permet de faire la discrimination entre ramollissement et glioblastome si la clinique et les examens neuroradiologiques restent hésitants.

L'hématome, principalement intracérébral, soulève aussi des difficultés diagnostiques. *En dehors des notions cliniques, la distinction repose sur des nuances* : absence d'hyperactivité lors des comptages précoces plus fréquente dans l'hématome que dans le glioblastome, maximum d'hyperactivité plus diffus dans le premier qui donne à ce maximum un aspect « en plateau » au lieu « du pic » habituel du deuxième cas. Des exemples sont présentés comportant les « courbes » tracées d'après les comptages point par point au contact du crâne et les gammaplanigrammes enregistrés dans les plans frontaux et latéraux. Le cas d'un patient examiné d'abord à l'aide du technetium avec comptages à 10 minutes, 1 heure, 24 heures, est montré, et on note la similitude des données obtenues avec la serumalbumine marquée à l'iode 131, avec comptages à 3 heures, 24 heures, 48 heures après l'injection du produit.

Le cas d'une patiente âgée de 39 ans suivie pendant plusieurs années pour crises faciales droites, est ensuite discuté. Un premier gamma encéphalogramme montre une asymétrie diffuse en faveur de l'hémisphère gauche, asymétrie que nous considérons comme suspecte, évoquant la possibilité d'astrocytome sans

Tableau 2

Tumeurs sus tentorielles	*Foyers gamma encephalographiques*		
	Précoces	Tardifs	Negatifs
Méningiomes (300)	80 5	16 5	3 5
Glioblastomes isomorphes (75)	44	41	15
Glioblastomes hétéromorphes (300)	21	75	4

qu apparaisse une localisation precise Le deuxieme gamma encephalogramme 18 mois plus tard revele un foyer caracteristique de glioblastome diagnostic compatible avec l evolution clinique aggravee *et les donnees ulterieures de l angiographie* Les traits distinctifs d un tel foyer avec ceux des tumeurs malignes *secondaires et des meningiomes sont soulignes* par des exemples

A cote des 70 % de foyers radioactifs de glioblastomes qui associent les caracteres d une maniere assez particuliere a cette neoformation 14 % ne sont plus suffisamment typiques pour permettre une conclusion d ordre etiologique Dans une proportion voisine de 10 % les foyers de glioblastomes se presentent avec les caracteres propres a une autre variete de tumeurs (Tableau 1) *L erreur la plus* frequente provient de l aspect inhabituellement circonscrit du foyer, associe a l apparition *tardive celui ci evoque alors* une tumeur de nature metastatique maligne Les glioblastomes responsables de ces fausses interpretations sont en general macroscopiquement bien limites clivables a l operation sur la majorite de leur pourtour au point qu ils apparaissent souvent aux neuro chirurgiens comme une metastase La presence d un kyste est parfois associee a la nettete des limites de l aire radioactive

Une autre sorte d erreur moins frequente mais plus grave pour la portee pronostique de la methode est de *confondre une hyperactivite* de glioblastome avec celle d un meningiome Ceci se produit quand le foyer est en meme temps precoce et nettement circonscrit (Tableau 2) L analyse de ces cas dans notre statistique a mis en evidence non seulement la nettete macroscopique du pourtour de la lesion apparemment non infiltrante mais encore a l examen histologique le degre de differentiation de la tumeur tel que la *plupart* de ces cas avaient ete classes comme glioblastomes isomorphes ou astrocytomes degeneres

L etude recente de 114 dossiers de malades porteurs d un glioblastome examines par angiographie et par gamma encephalographie dans le meme service temoigne une nouvelle fois de l interet que trouve le clinicien a associer ces deux methodes pour assurer le diagnostic de glioblastome avant de prendre une decision operatoire Tableau 3)

Tableau 3

Diagnostic de glioblastome dans 114 cas examinés par artériographie et gamma-encéphalographie

	Glioblastome		Nature incertaine	Total	
	Certain	Probable			
Diagnostic angiographique actuel					
Glioblastome	48		10	58 (51 %)	85 %
Tumeur maligne	24	2	13	39 (34 %)	
Diagnostic gamma-encéphalographique					
Nature incertaine	3			3 (2,6 %)	
Erreur	8		2	10 (8,7 %)	
Négatif	1		3	4 (3,5 %)	
Total	*84 (73,6 %)*	*2 (1,7 %)*	*28 (24,7 %)*	114	
	75				

Reste à aborder la discussion des données gamma-encéphalographiques dans l'extension en profondeur des lésions. Notre dispositif gamma-contact comporte une collimation prévue pour une bonne étude de la périphérie externe de la tumeur. Il se prête mal à l'étude en profondeur, au delà de 6 cm. Le prolongement d'une tumeur frontale vers les noyaux gris et l'hypothalamus ne peut être affirmé à l'aide de cette technique. Par contre le gamma-planigraphe est mieux adapté à l'observation en profondeur. L'absence de repères anatomiques visualisés par la radioactivité rend toutefois difficile l'estimation topographique de la diffusion. D'une façon générale l'extension d'une tumeur au corps calleux ne nous pose pas de problème. Nous avons pratiquement toujours pu la mettre en évidence par le comptage sur la ligne médiane et les zones voisines, et le gamma-planigramme vient à présent confirmer les cas douteux; dans deux cas seulement sur 31, le foyer était unilatéral et paramédian. Si l'atteinte du corps calleux est aisément accessible à la gamma-encéphalographie, il n'en est pas de même des gliomes frontaux et temporaux qui poussent leur prolongement vers la base. C'est là l'une des principales limites de la méthode dans l'étude de l'extension des tumeurs.

En *conclusion*, il semble qu'à l'heure actuelle la gamma-encéphalographie atteigne la limite de ses possibilités en ce qui concerne le diagnostic de présence

nature et extension des glioblastomes limites qui semblent imposees par les facteurs techniques et les facteurs biologiques Quels que soient les composes utilises les resultats sont comparables d une procedure technique a l autre Ils conduisent a des donnees probables sans caractere absolu pour ce qui est de la nature des lesions L emploi de cette methode en parallele avec l angiographie semble un des moyens les plus fideles et les plus fructueux de parvenir au diagnostic

RÉSUMÉ

L etude de plus de 500 cas de glioblastomes par la gamma encephalographie permet d etablir raisonnablement les limites actuelles de cette méthode dans le diagnostic des tumeurs cerebrales Une proportion de 2 % a 4 % des glioblastomes semble devoir echapper a la detection quels que soient les raffinements des procedures mises en oeuvre Les raisons en sont d ordre technique et biologique Reconnaitre la nature des lesions est possible dans la majorité des cas mais les criteres employes n ont pas une valeur absolue et ils sont a integrer dans le contexte clinique et radiographique Les causes d erreur les plus frequentes ont precisees Le choix des substances marquées semble avoir une certaine influence

SUMMARY

A material of 500 cases of glioblastoma examined with gamma encephalography was analysed in order to define the limitations of the method in the diagnosis of cerebral tumours However refined the techniques employed it seems that a proportion of 2 % to 4 % of glioblastomas escape detection due to technical or biologic factors The nature of the lesion can in most cases be determined but the criteria obtained are not decisive and have to be corroborated by the clinical and radiographic findings the most common sources of error are stated The results seem to be influenced by the choice of radioactive substance

ZUSAMMENFASSUNG

Ein Mat rial von 500 mit Gamma Encephalographie untersuchten Fallen von Glioblastom wurd n analysiert um die Zuverlassigkeit dieser Methode fur die Diagnos von Gehirntumoren abzu renzen Ab esehen von der Moglichkeit verfeinerte Verfahren anzuwenden h int es als ob 2 % bis 4 % der Glioblastome unentdeckt bleiben, was auf technische und biologi h Faktoren hinzufuhren sei Die Art der Lasionen kann meistens erkannt werden die Kriterien ind aber nicht ausschlaggebend und sollten mit den klinisch n und radio l h Befunde v rglichen werden Di haufigst vorkommenden Fehlerquellen werden di kuti rt Die Ergebnis e schienen in gewissem Mas e von d r Wahl der radioaktiven Sub tanz beeinflus t z i ein

ABTEILUNG FÜR ALLGEMEINE NEUROLOGIE, MAX PLANCK INSTITUT FÜR HIRNFORSCHUNG, 5 KÖLN MERHEIM, DEUTSCHLAND

ROENTGEN SENSITIVITY OF CEREBRAL TUMOURS AND SO CALLED LATE IRRADIATION NECROSIS OF THE BRAIN

by

K. J. Zülch

The effects of ionizing irradiation on the glioblastoma multiforme concern the changes in the tumour itself and the possibility of damage to the surrounding brain tissue. The question arises as to whether an effect is brought about through prevention of growth of individual cells or by necrosis of the whole tissue, perhaps as a result of interference with the blood supply. The mechanism of this irradiation effect may be caused by a disturbance of the barrier with exudation of certain substances from the vessels. These may either directly (dysorie of Schürmann), or indirectly through an allergic process, destroy the tissue. Hypoxia of the tissue, on the other hand, may be produced by the exudation of an albuminous substance; this is particularly the case in connection with radiation damage of the normal brain and spinal cord.

We feel there is some justification for assuming that the ideal effect of irradiation, namely the destruction of growing tumour cells, occurs only in two neuroepithelial tumours: the medulloblastoma and pinealoma. The possibility of a cure of such tumours by irradiation, in spite of the usual diffuse spread of metastases to the subarachnoid spaces, will be discussed.



Fig 1 Cells in the cerebrospinal fluid typical of pineal parenchyma (cf Del Rio Hortega) showing the nature of the blastoma ×500 and 1950 respectively

The irradiation effects upon the more important types of intracranial neoplasms will first be considered with emphasis upon the treatment of the glioblastoma multiforme

Gangliocytoma We have had no experience with irradiation of this tumour of the brain and know of no convincing report in the literature

Oligodendrocytoma and astrocytoma We have had one case of oligodendroglioma which was followed for eight years Neither of the operation specimens revealed evidence of definite radiation effects on the cells or vessels An irradiation effect cannot be deduced with certainty from the 8 year survival as similar biologic behaviour after re-operation on an oligodendroglioma has often occurred The total irradiation dose in this case was 16 000 rad

In another case of oligodendroglioma (8 000 rad to the temporal region) a severe radiation effect on the temporal white matter with cystic changes in the latter were observed This led to marked internal decompression The tumour, about 5 cm in diameter persisted, and its cells were unchanged (Zülch 1956, Fig 94)

In a further case a man, aged 52 with a fronto-medial oligodendroglioma four series of irradiations to 5 fields were given each series lasting about 4

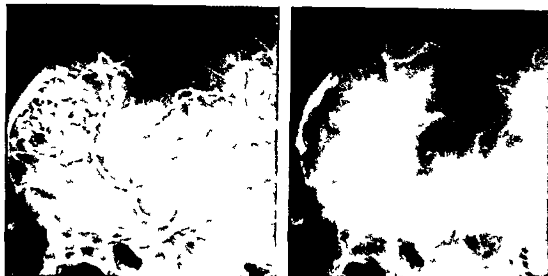


Fig. 2. Two angiograms of a midfrontal metastasis of a mammary carcinoma; the second taken after irradiation with 9 200 rad over two frontal fields

to 5 weeks, with a total of 30 000 rad. The patient survived for 5 years and 3 months from the beginning of the first treatment. At autopsy the tumour lay over a wide area of the cortex. Mild demyelination was present in part of the white matter. This could not be definitely attributed to the irradiation because peritumoral oedema may also produce this change. Careful examination of the specimen revealed no deviation from the normal appearances of an oligodendroglioma.

Finally, we may refer to a case reported in the literature (Eicke 1952), which after a total irradiation of 23 200 rad developed gross late necrosis of the white matter. The tumour remained about 3 cm in size and only in the crossfire of the different fields was there acute tissue necrosis with scarring. This agrees with the universal results reported in the recent monography of Bouchard (1966). Oligodendrogliomas must therefore, like astrocytomas, be regarded as relatively radiation insensitive tumours.

Consideration of the astrocytomas will be omitted from this communication (see Zulch 1963).

Polar spongioblastoma. A young boy aged 15, with a polar spongioblastoma of the posterior part of the third ventricle with extension into the mid brain, was given 4 600 rad to 5 fields over 3 months. The number of sessions is unknown. The spongioblastoma by the presence of several mitoses was recognized as being of a polymorphous, rapidly growing type. There were no signs of an irradiation effect, while the surrounding brain tissue clearly indicated commencing late ir-

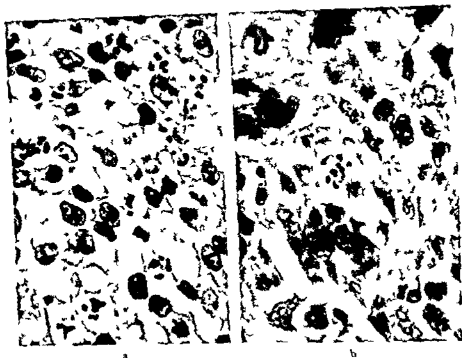


Fig 3 a) Glioblastoma Enormous number of often very atypical mitoses b) Fibrosarcoma 9 years after irradiation probably around 8 000 rad over one parietal field after excision of an extraventricular ependymoma × 100

radiation necrosis The total survival period after the irradiation was seven and a half months

Gross focal late irradiation necrosis was observed in a second case of spongioblastoma of the pons but the margins of the tumour had continued to grow

No indication appears to exist for irradiation of the polar spongioblastoma (according to our definition) i e the juvenile pilocytic astrocytoma of Dorothy Russell (Russell & Rubinstein 1963) This is in accordance with the experience of Bouchard This author refers to the glioma of the fasciculus opticus closely related to the above mentioned piloid astrocytoma whereby again obviously the polar spongioblastoma is meant These tumours have a very slow growth a fact that must be remembered when irradiation effects on such tumours are considered Bucy (1946) reported a case of a so-called astrocytoma of the cerebellum a spongioblastoma in which a cyst was emptied which was followed for 12 years with remission of the symptoms After this a massive residual tumour was visible which again was operated upon and again there was prolonged



Fig 4 Complete destruction of the white matter of both frontal lobes in an olfactory groove meningioma in a patient aged 50 years having received irradiation with 9 000 rad in 2 series with an interval of one month (Death occurred 5 years later from intercurrent disease)

healing In view of the markedly slow and favourable growth of this type of tumour it is difficult to analyse statistically the irradiation effect If these tumours are operated upon it will only be in instances of unfavourable site, admittedly frequent, such as when a short circuit (shunt) has to be performed Irradiation is indicated only in the presence of obstruction of the cerebrospinal fluid

Medulloblastoma Frequent reports have appeared in recent years of a very good effect of irradiation upon medulloblastoma RICHMOND (1953), for example, in 43 % of his series of children with medulloblastoma, after irradiation obtained a survival period of 5 years KAHN (1955), whose cases the present author himself examined histologically, had a 15 year survival Most of the remaining reports do not include such a successful irradiation effect even when combined with operation This is confirmed by BOUCHARD in his survey The detailed description of LINDGREN (1958) must be recognized as the first report on the necrosis of the tumour tissue Most of his success was obtained at the expense of damage of both occipital lobes (late irradiation necrosis), which can now be avoided with an appropriate technique

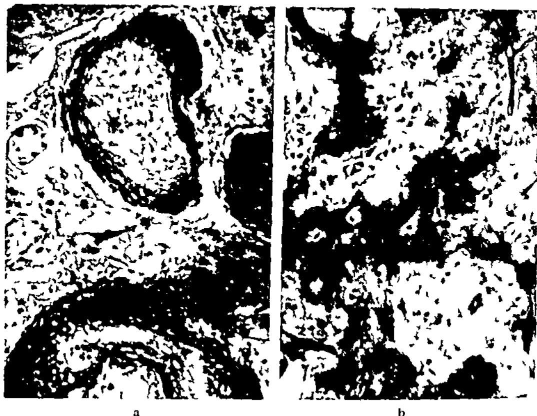
Pinealoma HORRAX & WYATT (1947) have reported on the good results with conventional roentgen irradiation

The present author can report a case of dramatic improvement as a temporary effect in one of our cases This was an 8 year old girl with a very small pinealoma and a large metastasis in the infundibular region (so-called ectopic pinealoma), demonstrated by pneumography as being 3 cm in size There was a gross diencephalic and endocrine as well as optical and ocular syndrome The subarachnoid space was not obstructed The pinealoma could be diagnosed with



Fig 5 a) A 200 g specimen of a growing late radionecrosis (operation for parietal recur e) b) Case of delayed rad onecros s Demyelination with preservation of the U fibers format on of a great cy t necrosis in the center Heidenhain Wolkes myel n stain

certainty by the shape of the cells in the cerebrospinal fluid (Fig 1) The child wa cachectic weighed 12 7 kg) and had to be artificially fed She was irradiated through 4 fields with 9 000 rad over 6 weeks There was good recovery and the hypothalamic and midbrain symptoms as well as those due to the ocular muscle paraly is disappeared The child could as a result go to school and was active for a long time as a completely healthy individual She survived altogether 5 years Because of recurrences a total dose of 23 500 rad through 4 fields to the chiasma regi n had to be given The child finally died with severe cerebellar signs an increa ing tetraparetic syndrome and towards the end a quadrigeminal syn drome Zulch 1963 Figs 1– 3)



a b

Fig. 6. a) Para-amyloid transudation around great veins in delayed radionecrosis. b) Diffuse spreading of the para-amyloid substance into the brain tissue. × 120

This final phase may be related to the growth of the primary pinealoma in the mid-brain, which was not irradiated, rather than to an irradiation effect on the brain during the irradiation of the ectopic metastasis. Repeat encephalography 2 years and 3 months after the first irradiation disclosed that the metastasis in the chiasma region had disappeared. The base of the anterior horn and the third ventricle were completely free from indentation. Further encephalography shortly before death was prohibited by the parents. Autopsy was not possible. The anisomorphic pinealoma should therefore also be irradiated with modern techniques.

Ependymoma. Only a slight irradiation effect has been observed in these growths. Para-amyloid substance, but scarcely any change in the tumour tissue was seen in one case. In another case there was a certain degree of sclerosis but this could not be definitely classified as an irradiation effect.

Glioblastoma multiforme. The irradiation effect on the glioblastoma multiforme forms the focal point of this communication.

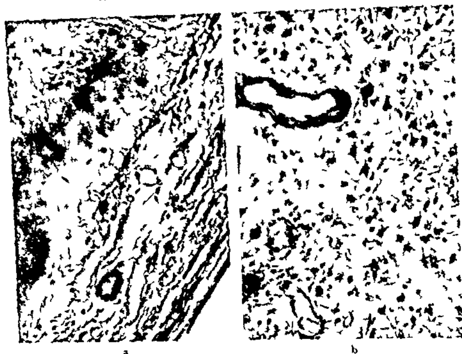


Fig 7 a) Para amyloid zone bordering the upper layers of the cortex towards the lepto meninges b) Proliferation of fibrillary astrocytes partly of a pleomorphic character in a demyelinated zone of radionecrosis × 120

An early effect was noted in a 55 year old patient with an angiographically proved right temporo-occipital tumour who was given an irradiation series of 1 600 rad over 9 days The patient died with raised cerebrospinal fluid pressure Inside the tumour and vessels lay para amyloid exudations readily distinguish able from other vascular changes in glioblastomas The necroses that were present could certainly not be interpreted as an irradiation effect because they belong to the morphologic ensemble of the glioblastoma The survival period as well as the irradiation dosage, was probably too small to have produced such an effect

Another patient, aged 59 with a glioblastoma multiforme of the temporal pole was irradiated with 6 700 rad to 2 fields over 21 days The patient died 42 days later At autopsy early para amyloid deposits were seen in the vessels Amoeboid glia e g around the capillaries represent early changes that may also be seen in the transudation zone of the para amyloid material

A third patient aged 56, with a right temporo medial glioblastoma multi forme received 10 600 rad to 6 fields over 31 days At autopsy 16 days following

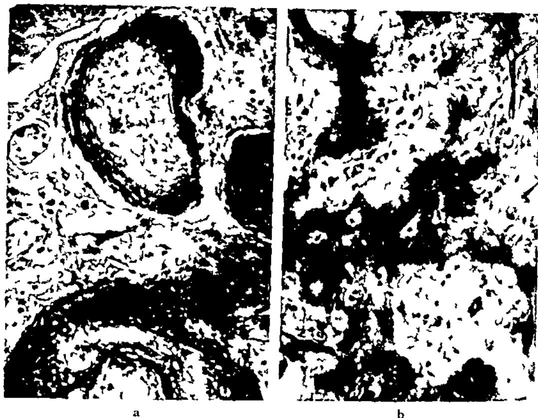


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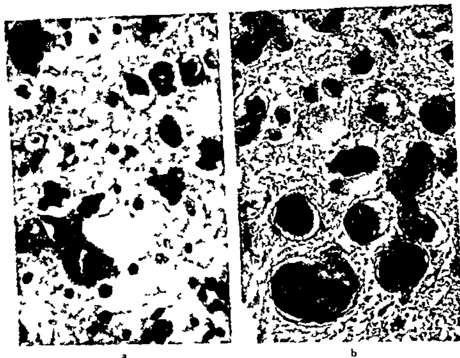


Fig 9 a) Multinucleated and giant astrocytes in experimental radionecrosis ×500
b) Angioma like proliferation of new vessels in experimental radionecrosis ×50

pletely destroying the tumour and run the risk of late necrosis occurring in adjacent cerebral tissue or to give a lower dose in which case there will be less damage to cerebral tissue but the tumour may not be completely destroyed

Metastases Extensive experience of the irradiation of metastases and follow up of the degeneration of the vascular structures angiographically have led us to believe that the irradiation effect was produced by thrombosis which caused massive necrosis Small malignant foci often escaped notice however The danger of increased malignancy will be discussed later (Fig 2)

Extracranial tumours meningioma and neurinoma Scarcely any indication for the irradiation of these tumours exists A case in which because of war conditions irradiation was carried out conventionally probably with 9 000 rad over one month in 2 series concerned an olfactory groove meningioma the irradia



Fig 8 Experimental radionecrosis in a rabbit 10 months after a single dose irradiation with 3 000 rad *conventional roentgen rays a) Radionecrosis and formation of cyst b) Space oc cupying cyst*

the treatment, massive necrosis in the interior of the tumour, a possible irradia tion effect, was evident The surrounding brain showed no deviation from the normal, no change in the tumour cells could be recognized The irradiation ef fect was in this case uncertain

Finally in a patient with a left fronto basal glioblastoma, cortical necrosis occurred 14 days after an operation in which radiocobalt pearls were placed in the wound cavity for 24 hours (cf KLAR et coll 1954) These had not destroyed all parts of the tumour there was transudation of material similar to the para amyloid substance in late irradiation necrosis No comparable case has so far been encountered

In summary the earliest irradiation effects occurred 31 days after irradiation with 10 600 rad to 6 fields This however, is not quite definite, because gross central necrosis is not rare in glioblastomas and because no change was noticeable in the tumour cells Perhaps and the para amyloid extravasation present in two further cases speak for this a change in the vessel wall may have actually taken place e g an increased tendency to spontaneous thrombosis This is the principal irradiation effect in glioblastoma An effect on the cells such as has definitely been demonstrated in the pinealoma, were not present in the glioblastomas

The results are in agreement with those reviewed by BOUCHARD though it cannot be denied that in individual cases a prolongation of life may occasionally be obtained The object must be to necrose the glioblastoma massively but obtain relative preservation of the surrounding cerebral tissue How far this is possible technically is open to discussion The problem by irradiation is to determine the quantity of irradiation to be given whether to give a dose sufficient for com

Development of irradiation cancer

A young female aged about 14 years had an ependymoma of the cerebral hemisphere which was radically removed Six years later a true fibrosarcoma occurred in the ring scar of the dural flap and led to death (ZÜLCH 1952) Late irradiation necrosis was evident deep down in the brain substance but there was no trace of the primary ependymoma The irradiation was conventional and had involved up to 8 000 rad (LORENZ) without any unusual features (Fig 3b)

Cases of NOTZLI & MALAMUD (1962) MANN et coll (1953) RUSSELL & RUBINSTEIN (1963) and TERRY et coll (1959) as well as a case of WENDE (1962) appear in the literature It is interesting that the tumours were always fibrosarcomas which histologically are similar or identical BERG & LINDGREN (1958) in their experimental work with irradiation of normal rabbits have observed osteosarcomas developing in the region treated

Indications for irradiation based on morphologic experience

1 Medulloblastoma and pinealoma cells can definitely be killed

2 Metastases thrombosis of the neoplastic vessels can be produced and necro is thus be obtained The effect under (1) i e destruction of tumour cells may also apply

3 Similar considerations apply to the sarcomas and especially the reticulosarcoma which appears to have cells that are particularly sensitive

4 A relative indication is the irradiation of a glioblastoma where the type of effect and the results have not yet been fully reviewed

Irradiation of the polar spongioblastoma ependymoma astrocytoma and oligodendroglioma is not recommended operation only and in cases of recurrence re-operation followed by irradiation are preferred

It is nece ary to emphasize that it is difficult to establish irradiation *effects by a purely* tatistical investigation without biopsy In the above review of the morphology *and biology of glioblastomas* it was stated that there are two types of malignancy true malignancy of growth of the tumour and clinical malignancy which can be deduced only *from statistics* The collection of series of morphologically controlled cases such as LINDGREN has been able to present in his monograph is of course just as important as large statistics

Two special conditions *produced by ionizing* irradiation must be considered under clinical malignancy Late irradiation necro is may lead to a space-occupying or an atrophic *pro ess This will* be described below in detail Both possibilities le sen the value of any purely statistical observation because an apparent recurrence may be an *expanding* late irradiation necrosis of the white

tion was obviously given with a bilateral fronto temporal approach The tumour was practically unchanged although perhaps a little more hyalinised than usual On the other hand, the entire frontal region (ZULCH 1960) was destroyed by bilateral irradiation necrosis, the myelin sheaths were lost, and the tissue had been changed into a cystic gelatinous mass This resulted in an increased intra cranial space due to marked internal decompression The patient developed a parallergic reaction suggesting encephalitis He passed into status epilepticus with a fatal outcome (Fig 4)

Malignant mesodermal tumours We could follow a patient, aged 52, with a monstrocellular sarcoma in the left parietal region, who received in three irradiation series a total of 22 400 rad, made up of 3 700 over 15 days, followed 14 days later by 11 400 rad over 27 days, and finally 3 years and 4 months later 7 000 rad over 25 days The operation specimen 8 days after the last irradiation and 4 years and 3 months after the beginning of the first irradiation disclosed an obvious necrotizing effect An actual and statistically favourable irradiation effect had been obtained

A post operative survival as long as two and a half years has been encountered in an exceptional case of a small sarcoma which was completely removed at operation These tumours usually possess the same malignancy as the glioblastoma multiforme

Of the remaining sarcomas the reticulo sarcoma of the brain and the spinal epidural space are particularly irradiation sensitive (BINGAS & ZULCH 1964)

Undesirable effects of ionizing irradiation increased malignancy

Foci of increased malignancy with a higher number of mitoses than previously encountered in any other human tumour were observed in the vicinity of large necroses in two irradiated glioblastomas (Fig 3a) The number of mitoses was practically the same as that of the cells (ZULCH 1960) It would appear that this was due to an increase in the rate of growth, similar to that reported by NETSKY (1956) in the irradiation of cell cultures This author reported a depression of growth later followed by so-called biphasic growth with a speeding up the original slower rate of growth was thus again achieved and later exceeded

A similar experience dates from before the Second World War, and came from Tonnis s Clinic in Berlin where prolonged survival was attempted by the introduction of radium needles (LORENZ 1949) It was perhaps scarcely a coincidence that in both these two cases the tumour growth was speeded up to a degree not previously encountered Within six months gigantic recurrences, almost the size of a fist were removed six times by operation (ZULCH 1940)

operation at which a 200 g mass was removed The patient has since remained free from symptoms Investigation of the large portion of cerebral tissue excised revealed total necrosis of all the white matter but no blastoma infiltration the cortex was unaffected (Fig 5a)

A similar case was described by LOWENBERG SCHARENBERG & BASSET (1950) (6 000+3 600 rad 22 months later) which also presented signs and symptoms of a space occupying process At operation the irradiation-damaged area appeared macroscopically like a glioma (similar to the appearances described by SCHOLZ & HSU)

DUGGER et coll (1954) have also described a case in which space-occupying necrosis occurred 26 months after irradiation This case also seemed to be one of a glioma and the records indicated that irradiation doses of 6 000 rad over 12 days 3 600 rad over 24 days and 2 340 rad had been given The patient died 9 years later when localized glio is with atrophy principally affecting the white matter was revealed

The pathogenesis of late irradiation necrosis Clarification of the pathogenesis may be obtained from the morphology of experimental late necrosis in animals The data that follow were derived from observations in man and in a series of experimental irradiation injuries in rabbits by the method of BERG & LINDGREN which HARDER (1965) published in a doctorial thesis *It was possible in these* experiments with animals also to produce expanding necrosis cysts (ZULCH 1963 *Figs 8 to 11*) perhaps to some extent similar to the expanding space-occupying late irradiation necrosis described We believe with SCHOLZ, to have *established* that damage of the permeability of blood vessels underlies the lesions and that this produces a substance designated as para amyloid (ZULCH 1960 1963) We do not think that the conclusion of SCHOLZ can be maintained however viz that because of a change in vascular permeability ischaemia develops in the tissues and causes secondary necrosis because the vessels are no longer patent for gases and nutritive material so that the tissue becomes anoxic HARDER s experimental work repeatedly demonstrated that quantitatively a para amyloid change in the vessels remained in the background and that destruction of the myelin sheaths and particularly an early and gross change in the glia were the outstanding features The astroglia for example proliferates in a manner which results in the formation of multinuclear giant cells as evident otherwise only in malignant tumours (Fig 9)

Animal experiments reveal damage only in the white matter The cortex is damaged only if just as in man it lies in the cross fire of the irradiation of many fields receiving excessive doses as in EICKE s case This occurred in a small circumscribed region in the case of the olfactory groove meningioma the corte

matter, while a loss of volume of the white matter by irradiation necrosis may produce an internal decompression space and thereby simulate post irradiation healing

Late irradiation necrosis

This has received particular attention in the last decade (ARNOLD et coll, BAILEY et coll, BOUCHARD, LINDGREN, LOHR & VIETEN, SCHOLZ et coll, ZEMAN, ZULCH 1956, 1960, 1963) It appears that the first case of irradiation late necrosis in man was described by FISCHER & HOHLFELDER (1930) The case was later described in more detail by KALBFLEISCH (1946) SCHOLZ & HSU (1938) described the brain of a schizophrenic who was given irradiation elsewhere in an experimental study of the blood cerebrospinal fluid barrier SCHOLZ (1934) tackled the condition by experimental work and MARKIEWICZ (1935) reported these findings in detail The observations of PENNYBAKER & RUSSELL (2 300 rad to a rodent ulcer of the skin) are well known The present author encountered late irradiation damage of the brain in 26 autopsies of his material These included 6 oligodendrogliomas and astrocytomas, 1 spongioblastoma, 3 ependymomas, 8 glioblastomas, 2 metastases, 2 meningiomas, 3 monstrocellular sarcomas and 1 unclassified process Since 1956 he has repeatedly referred to the danger *of late irradiation necrosis of the white matter* (1960, 1963) and emphasized its peculiar susceptibility and on the other hand the relative immunity of the grey cortex

Time dose relationships have been defined by BERG and LINDGREN These *authors encountered late irradiation necrosis of the white matter only* in some of their cases, this was however observed after doses that up to then were lower than those used in conventional therapy COCCHI reported a case in which a focal dose of 3 500 R to a pituitary adenoma produced late irradiation necrosis *which destroyed the overlying temporal lobe on the non operated side*

I mentioned earlier that late irradiation necrosis can lead either to an increased or a decreased volume of the intracranial space The olfactory groove meningioma (Fig 4) exemplifies how the gelatinous scarred and shrunken white *matter may lead to a loss of space*

In contrast to the above mentioned feature I may relate a case of a 24 year old woman earlier reported upon (ZULCH 1960, 1963) in whom a right parieto occipital tumour was partially resected Post operative irradiation with 6 000 rad was *followed after 3 years and 4 months* by a second series of 2 500 rad, and a few months later by a third series of about 3 700 rad, a total of over 10 000 rad One year after operation the normal birth of a daughter was followed in the next year by normal birth of a boy Five years after operation there were signs of raised intracranial pressure and epileptic attacks indicating the necessity of further

ly strangled by surrounding scar tissue several millimetres thick No signs of a para amyloid substance could be recognized histologically The spinal cord was softened from a ring scar originating in the leptomeninges and dura which obviously had led through constriction to liquefaction of the spinal cord In addition there was probably thrombosis of the anterior spinal artery which had become recanalised It is probable that all the malignant cells had been destroyed by the irradiation i e the desired effect had been achieved The presence of tumour cells in the leptomeninges and dura concentrically around the spinal cord had led to scarring of the infiltrated region secondarily causing strangulation of the spinal cord The patient had thus been protected from growth of the malignant tumour (for 14 years and 6 months) an effect at the cost however of softening of the spinal cord This did not arise from late irradiation necrosis but through scarring of the primary tumour (a detailed report will follow)

This case clearly indicates the discrepancy between the purpose of therapy and the actual effect of the irradiation The goal can often only be achieved at the expense of secondary damage but how far this occurs with the glioblastoma should be discussed

SUMMARY

The effects of conventional irradiation on different types of intracranial tumours are described and indications for radiotherapy are given on the basis of morphologic observations The possibilities of late irradiation damage to the brain and spinal cord are emphasized such damage may suggest either recurrence or give a false impression of cure In the absence of correlation with autopsy and isotope data and operative and angiographic findings these facts should be taken into account in all statistical evaluations of the results of irradiation therapy

ZUSAMMENFASSUNG

Die Wirkung konventioneller Rontgenbestrahlung auf die einzelnen intrakraniellen Geschwulstarten wird besprochen und aufgrund morphologischer Beobachtungen werden Folgerungen fur die Indikation zur Rontgenbestrahlung gezogen Die Moglichkeit der Strahlen Spatschadigung des Gehirns und Ruckenmarkes wird betont Diese Spatnekrose kann entweder ein Recidiv oder Heilung vortauschen Dies ist bei allen statistischen Untersuchungen uber Strahlenwirkung ohne autoptische operative angiographische und Isotopenkontrolle zu berucksichtigen

RÉSUMÉ

L auteur decrit les effets de l irradiation par les moyens classiques sur differents types de tumeur intra-craniennes et definit les indications de la radio-therapie sur la base des signes morphologiques Il insiste sur la possibilite de radio lesions retardees du cerveau et

remained otherwise intact These findings thus differ from those of WACHOWSKI & CHENEAUIT (1945) A working hypothesis might be that an allergic auto-immune process occurs, with primary damage of the myelin sheaths, similar to that which MARKIEWICZ, and BERG & LINDGREN have envisaged as a basic process According to this concept, a substance which damages the myelin sheaths escapes from the vessels The changed myelin then forms an antigen which evokes antibodies against the myelin, leading to its partial destruction An auto-immune disease in which the glia also plays a certain but obscure role thus occurs Proliferation of dysmorphic astroglia is a prominent feature in animal experiments Our findings in man suggest that this process of demyelination may lead to a kind of autonomous disease, perhaps even progressing in the non irradiated parts

In spite of all this, certain questions relating to the pathogenesis remain unanswered In many instances human subjects remained free from late irradiation necrosis in spite of high dosages Moreover, the condition is almost always confined to the white matter Late irradiation necrosis may be a result of peritumoural oedema but in animal experiments never appears to arise in this form The same time intervals and similar morphologic appearances as in man may apply but in about a *fifth of the animals no late irradiation damage occurs* (BERG & LINDGREN) Constitutional factors may perhaps first set this auto-immune process in action This variable latency in the occurrence of late damage may extend from the 7th to the 9th month (the predilection time) (e g the case of PENNYBAKER & RUSSELL) but also up to 5 years In one of the cases beyond 5 years slight extension of the process in the cortical region was evident (ZULCH 1956 Fig 24)

The extensive white matter of the spinal cord is as radio sensitive as that of the brain The irradiation effect is particularly prominent (KRISTENSSON et coll 1967) because the concentration of so many white tracts in a thin segment usually produces a transverse lesion after irradiation of external organs e g hypopharyngeal carcinoma Care in the clinical diagnosis as in the statistical evaluation of irradiation effects in cerebral tumours, must however be exercised

A case of post irradiation damage of the spinal cord that clearly indicated the difficulties of a roentgen therapist was recently reviewed An operation had been performed on an unclassified tumour of the arachnoid and the dura of the spinal cord The material was reported as unclassified but a similarity with some thyroid neoplasms and certain meningiomas was emphasized The tumour grew in an infiltrative manner and was malignant It was finally irradiated in a conventional manner with 5 500 rad A transverse symptomatology, apparently as a result of late irradiation necrosis developed a few months later

The patient survived fourteen and a half years when the morphologic changes indicated that the spinal cord in the irradiation zone had become partial

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de la moelle ces lésions peuvent faire penser soit à une récidive soit donner une fausse impression de guerison En l'absence de corrélation avec les données de l'autopsie et par les isotopes et avec les constatations opératoires et angiographiques ces faits doivent etre pris en considération dans toutes les etudes statistiques des resultats du traitement par les radiations

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TUMOR EXTENT AS A DETERMINING FACTOR IN RADIOTHERAPY OF GLIOBLASTOMAS

by

SIMON KRAMER

In spite of improvements in radiotherapy equipment and techniques in recent years we are unable to cure the great majority of highly malignant gliomas of the brain For establishing the cause of failures we have two propositions to consider (1) that the highly malignant glioma is biologically so constructed that it is radioresistant at a dose level tolerated by normal brain tissue and (2) that our treatment techniques may inadequately irradiate all the tumor tissue present This paper is concerned with the second aspect

Some years ago while working at the Royal Marsden Hospital, I was engaged in the treatment of a large number of patients with brain tumors These patients formed part of a controlled study to determine the value of postoperative irradiation for intracranial gliomas (PENMAN 1954) A number of these patients mostly with astrocytic gliomas grades III and IV died shortly after admittance for radiation therapy and usually before an adequate amount of treatment could be given Thirty such cases came to autopsy and formed the basis of a study undertaken by CONCANNON and myself to compare the estimated size of the tumor to be irradiated with its true extent A full report of this study has been published earlier (1960) The complete clinical notes roentgenograms and the preserved brains of these patients were available for study Localization of

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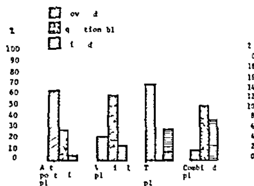


Fig 1 Graphic representation of the number and percentage of tumors adequately included questionably included and missed in the volume irradiated each plane considered separately and then for all planes combined

the tumor and estimation of its size for the purpose of radiation therapy was based primarily on contrast roentgenologic examinations In addition, the clinical and operative findings were taken into account The size and localization of the tumors as indicated by these studies were compared with the actual size and location as shown at post mortem examination We modified BULL & ROVIT's classification (1957) of the result of roentgenologic localization of brain tumors more adequately to suit the purpose of the radiation therapists This is important since probably an appreciable part of the tumor will be underdosed or missed completely if any portion of the tumor lies outside the area delineated by the radiologist

Our classification of results in the roentgenologic diagnosis of brain tumours is as follows

1 *Excellent* the tumor accurately and completely localized

2 *Good* major portion of the tumor localized, less than 20 % of tumor outside but closely adjacent to the area delineated by the radiologist

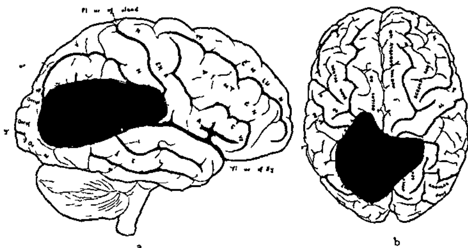
3 *Poor* more than 20 % of the tumor outside the indicated volume, tumor distantly removed from the area indicated study inadequate to demonstrate tumor or localize tumor

The roentgenologic diagnostic accuracy in the 29 patients for whom roentgenograms were available was as recorded below

Excellent	4 cases	13 8 %
Good	11 cases	37 9 %
Poor	14 cases	48 3 %

In almost half the number of cases the roentgenologic localization was so poor that at least 20 % of the tumor or more was outside the volume indicated by the roentgenologic examination

A review of the time interval between the contrast studies and the death of



a b

Fig 2 Diagrams of tumor extent in a patient as determined prior to therapy (a) and at utopsy (b)

the patients showed that 50 % of them had died within 30 days of the study being performed and all within 78 days so that it is unlikely that the tumor had extended at all between the time of the study and death Conversely it is un likely that the radiation therapy given to some of these patients had decreased the size of the tumor materially in this group of patients since only 6 completed the planned course of therapy

Our treatment policy at that time was to irradiate patients with malignant gliomas through medium sized portals in the hope of being able to deliver a large dose to a relatively small volume The desired dose was 5 500 to 6 000 R to be delivered in 6 to 7 weeks As a rule two lateral portals measuring 10 cm×8 cm and a superior portal measuring 10 cm×6 cm were employed so that a cylinder of tissue approximately 8 cm×8 cm×10 cm was included in the high dose vol ume The volume however was adjusted to include the tumor as indicated by the roentgenologic examination described above

In 21 of these patients who died so quickly after admission to our hospital, radiation therapy had either been planned or commenced and in these patients we were able to compare the extent of the planned treatment volume with the actual extent of the tumor in the post mortem specimen We chose as the actual tumor volume that needed to encompass the gross extent of the tumor surrounded by a 1 cm zone of grossly normal tissue around the tumor as a minimum margin of safety Microscopic extension of the tumor although almost certainly present



Fig 3 Sections of the brain of the same patient as in fig 2 to show the extent of the tumor

to a large extent, was neglected in the study since this could only increase the degree to which we failed to cover the tumor adequately We also assumed that the setting up of the treatment fields would have been entirely accurate in order to optimize the conditions of tumor coverage Isodose curves for the planned fields were plotted in the antero posterior, vertical and transverse planes and the gross tumor extent in each dimension as determined at post mortem examination of the brain was compared with the isodose curve for the corresponding plane Our results were analyzed as follows

Tumors were considered adequately covered by the treatment plan if in each plane the gross extent of the tumor and the 1 cm zone around it was included within the isodose curve Tumor coverage was considered questionable if there was the possibility that a portion of the tumor or its surrounding margin was outside the irradiated volume The tumor was considered missed if a portion of the tumor or of the 1 cm margin was definitely not within the treated zone The result of our analysis was that out of the 21 patients with completed treatment plans, the tumor was covered adequately in only two Tumor coverage was questionable in 11 and a portion of the tumor was definitely missed in 8

Fig 1 is a bar diagram of these findings for each plane separately and all planes combined and it will be seen that particularly in the vertical plane and the transverse plane the planned volume was inadequate and that in the vertical plane, coverage was questionable in a large number of patients Leaving aside the question of microscopic infiltration, even a study such as ours of the gross pathology confirms the well known fact that gliomas spread beyond the confines of an anatomic area such as a lobe of the brain and that the highly malignant gliomas are almost invariably larger and more extensive than was suspected in the clinical and roentgenologic examination Laterally placed tumors extended mainly in an antero posterior direction more centrally placed tumors not infrequently spread across the midline (9 patients), and two patients in this series had an unsuspected second glioma in the same hemisphere in one of the patients and on the opposite side in the other

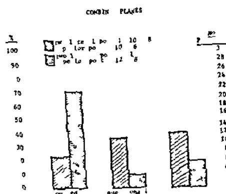


Fig 4 Graphic comparison of results for medium field versus large field technique for all planes combined

A diagram of the suspected lesion in a patient considered to have a unilateral parieto-occipital tumor is shown in Fig 2 Examination of the fixed brain disclosed that the tumor extended massively into the opposite hemisphere (Fig 3)

Since most of the treatment plans were for the medium sized fields described above we next made a study of the tumor coverage which would have been obtained in the 30 patients with this technique and compared this with the results which we might have achieved by a large field technique For the purpose of this study the medium field technique was again defined as two lateral 10 cm×8 cm portals and a superior 10 cm×6 cm portal whereas large fields were defined as two lateral 12 cm×9 cm portals and a superior 12 cm×8 cm portal The same conditions were applied to this study as in the analysis of the portals actually used It will be recognized that the medium sized field technique gives us a high volume cylinder of approximately 8 cm×8 cm×10 cm whereas the large volume technique gives us a cylinder of 9 cm×10 cm×12 cm a volume almost double The result is graphically presented in Fig 5 This figure shows that had the larger fields been used the tumor would have been adequately covered in nearly three-quarters of the patients instead of less than one-quarter where the smaller portals were used Those in whom the tumors were missed would have been reduced from more than one third to one fifth and those in whom coverage was questionable would have been reduced from one third to one tenth Even so one fifth of the tumors would have been missed and this leads me to believe that in this group of highly malignant gliomas the whole intracranial content has to be irradiated

It must be stressed that this is a highly selected group of patients since all of them died soon after admission and almost all of them had extremely malignant tumors Clearly these patients may have had larger and more rapidly growing tumors than others who would have survived for longer periods of time



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We conclude that with our present method of localization and knowledge of spread of gliomas there is no place for small or medium volume radiation therapy in the treatment of the highly malignant tumors. I believe that if there is to be hope of success the whole of the intracranial contents has to be irradiated. This study does not answer the question whether roentgen therapy can be effective for these tumors with large volume irradiation. I believe the question answered here is that radiotherapy is unlikely to be effective if smaller volumes are treated. Such failure could be caused solely through inadequate coverage of the tumors.

Acknowledgements

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SUMMARY

Failure to cure highly malignant gliomas may be due to an underestimate of the tumor extent. Twenty-one patients were planned for irradiation (chosen target volume as a rule 10 cm×8 cm×8 cm) but death occurred before effective therapy was given. When the treatment plan was compared with the tumor extent in the autopsied brain, only two out of the twenty-one patients were found to have had adequate tumor coverage. If the target volume had been doubled (12 cm×10 cm×9 cm) one fifth of the patients would still have had inadequate tumor coverage. We conclude that the whole brain should be irradiated for glioblastomas.

ZUSAMMENFASSUNG

Ein Misserfolg in der Behandlung hochmaligner Gliome mag auf eine fehlerhafte Beurteilung der Ausbreitung des Tumors beruhen. Strahlenbehandlung wurde für 21 Patienten planiert (Feldgrösse meistens 10 cm×8 cm×8 cm), aber die Patienten starben bevor die Radiotherapie effektiv durchgeführt werden konnte. Bei Autopsie des Gehirns in diesen 21 Fällen zeigte es sich, dass die Behandlungsplanung nur in zwei Fällen den ganzen Bereich des Tumors umfasste. Falls die Feldgrösse verdoppelt wäre (12 cm×10 cm×9 cm), so würde man in einem Fünftel der Fälle immernoch eine unzureichende Tumorbestrahlung erreicht haben. Es erscheint in Fällen von Glioblastom, dass das ganze Gehirn bestrahlt werden sollte.

RÉSUMÉ

L'échec du traitement de gliomes très malins peut être dû à une sous-estimation de l'étendue de la tumeur. L'auteur a établi le plan de traitement de vingt et un malades (le volume cible choisi était en règle de 10 cm × 8 cm × 8 cm), mais ces malades sont décédés avant d'avoir reçu un traitement efficace. La comparaison du plan de traitement avec l'extension de la tumeur dans le cerveau autopsié a montré que le volume irradié n'englobait convenablement la tumeur que chez deux malades sur les vingt et un. Si on avait doublé le volume cible (12 cm×10 cm×9 cm) un cinquième des malades auraient encore eu un volume d'irradiation inadapté. L'auteur conclut qu'il faudrait irradier le cerveau entier pour les glioblastomes.

Fig 1 Repartition topographique des glioblastomes multiformes suivant la frequence des localisations

Fig 2 Repartition des glioblastomes multiformes suivant l age

Fig 3 Irradiation par radiothérapie conventionnelle à 200 kV suivant la technique des cinq champs

SERVICE DE RADIOLOGIE (PROFESSEUR J LEGRE), HÔPITAL DE LA TIMONE, MARSEILLE, FRANCE

L'IRRADIATION DES GLIOBLASTOMES MULTIFORMES

Résultats respectifs de la radiothérapie conventionnelle et de la gammathérapie à propos de 87 cas

par

J LEGRE, R AMALRIC et J PADAUT

A la suite de nos travaux publiés au Symposium de Neuroradiologie de New York 1964 et du Congrès International de Radiologie de Rome 1965, nous avons repris l'étude exclusive du traitement post opératoire des glioblastomes multiformes par les radiations portant sur 87 cas

Définition anatomique des glioblastomes dans le cadre des gliomes KERNOHAN propose de classer les tumeurs gliales en quatre groupes, le grade I répondant à la forme bénigne le grade IV à la forme cytologiquement la plus maligne qui dans le cas particulier des tumeurs astrocytaires, aboutit à l'image du glioblastome multiforme

Le glioblastome multiforme réalise la forme la plus évocatrice des gliomes malins

C'est macroscopiquement une tumeur volumineuse, molle granuleuse très nécrotique, parsemée d'hémorragies Son étude histologique révèle un polymorphisme extrême en présence de cellules jeunes, allongées ou globuleuses, à cytoplasme peu abondant, noyaux atypiques, parfois plasmodiaux fréquemment en mitoses

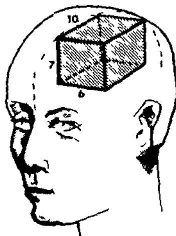


Fig 5 Surface des champs et volume cible (400 ml)

Repartition des glioblastomes multiformes

Suivant le sexe Les glioblastomes multiformes sont presque trois fois plus frequents chez l homme que chez la femme 64 hommes soit 77 % et 22 femmes soit 27 %

Suivant la localisation topographique Il n y a pas de predominance suivant l hemisphere 43 pour l hemisphère droit et 42 pour l hemisphere gauche

Pour les glioblastomes hemispheriques (Fig 1) on observe une nette predominance de la localisation temporale 27 cas Viennent ensuite les localisation frontales 18 cas et Rolandique 17 cas donc a peu pres a egalite

Les autres localisations sont beaucoup plus rares

Nous n avons observe que 5 cas de glioblastomes sous-tentoriels deux a localisation vermienne et trois à localisation hemispherique

Suivant l age (Fig 2) Les glioblastomes multiformes peuvent s observer a tous les ages mais ils predominent tres nettement dans les trois decades de 30 a 60 ans avec maximum dans la decade 50 a 60 ans

Technique

Radiotherapie conventionnelle a 200 kV Jusqu en 1958 nous avons utilise la technique classique à 5 champs comportant quatre feux croises orthogonaux dans un plan transversal (trois homolateraux et un controlateral) et un feu vertical bregmatique (Fig 3)

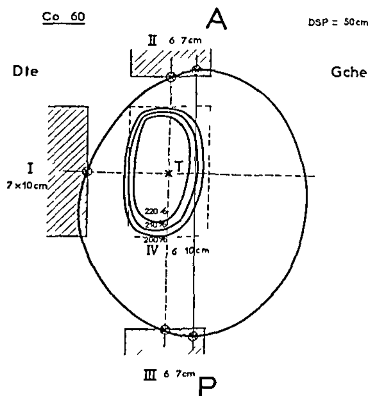


Fig 4 Irradiation par hautes énergies (cobalt 60) suivant la technique des quatre champs hémisphériques homolatéraux

Deux éléments fondamentaux le caractérisent présence de foyers nécrotiques au pourtour desquels les cellules se disposent en palissades pour réaliser des pseudo rosettes, images d angiogenèse avec aspect glomérulé des vaisseaux pathologiques

Il existe, d autre part, des tumeurs beaucoup plus organoïdes les formes malignes des astrocytomes, les astroblastomes, les oligodendroblastomes et les épendymomes

Il convient de souligner que dans un glioblastome authentique peuvent s observer un certain nombre de contingents astrocytaires protoplasmiques ou fibrillaires et oligodendrocytaires

Il faut donc retenir l intrication éventuelle de types cytologiques très différents au sein d une même tumeur On ne saurait donc, de ce fait, établir de cloisons étanches entre ces différents types pathologiques en présence Aussi est on amené à regrouper sous le terme général de gliome malin l ensemble de ces types

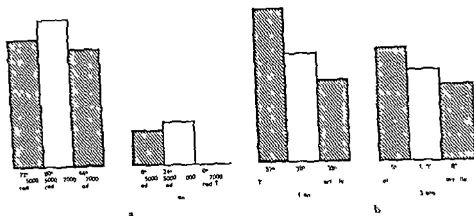


Fig 7 Survie therapeutique en fonction de la dose (dose optimal entre 5 000 et 7 000 rad/tumeur) (a) et survie therapeutique en fonction du volume irradie (b)

A deux ans il est presque cinq fois moindre 9 %

A trois ans il est plus de dix fois plus faible Il ne reste plus que 4 % des malades en vie

Survie therapeutique en fonction de la nature des radiations roentgen et gamma (Fig 6b)

A un an le benefice net en faveur des rayons roentgen est de 58 % contre 23 % par les rayons gamma — donc gain de 35 %

A deux ans meme constatation favorable mais le gain n est plus que de 10 %

A trois ans 8 % des malades traites par rayons roentgen sont encore en vie alors que tous les malades traites par cobalt sont decedes

Nous avons observe deux survies exceptionnellement longues de glioblastomes traites par radiotherapie l une de 52 mois (dose 5 000 rad/tumeur) et l autre de 44 mois (dose 5 000 rad tumeur) Surpris de ces resultats les coupes histologiques ont ete revues par plusieurs anatomo pathologistes dont les conclusions ont ete identiques et formelles en faveur d un glioblastome

Survie therapeutique en fonction de la dose tumeur (Fig 7a)

A un an les meilleurs resultats (80 %) sont obtenus avec des doses de 5 000 a 7 000 rad tumeur Au-dessous de 5 000 rad il y a une difference de 8 % Au dessus de 7 000 rad il est remarquable que la difference ait atteint 16 % Les plus mauvais resultats sont donc obtenus avec des doses superieures a 7 000 rad/tumeur

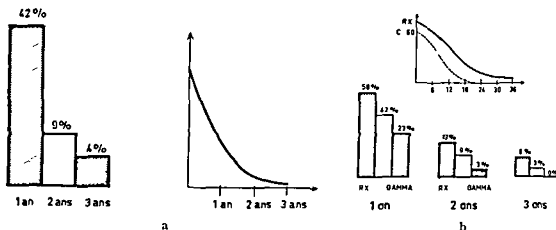


Fig 6 Survie therapeutique globale (a) des glioblastomes et en fonction de la nature des radiations roentgen et gamma (b)

Dans ces conditions, le rendement a la tumeur etait de 180 %, pour un volume cible de 480 ml

La dose tumeur etait en moyenne de 7 000 rad avec etalement de trois mois et une dose tumeur quotidienne de 75 rad/tumeur

Cobalt 60 ou caesium 137 Nous avons tente, au debut, l irradiation des tumeurs cerebrales par deux feux transversaux opposes, mais les resultats des survies therapeutiques nous ont rapidement montre l insuffisance de cette technique

Nous avons alors adopte une technique d irradiation strictement hemispherique, a quatre feux, comportant trois feux orthogonaux transversaux homolateraux et un feu vertical (Fig 4)

Le rendement a la tumeur est alors de 220 %

Surface des champs et volume cible (Fig 5) Nous avons adopte les surfaces d irradiation suivantes feu frontal et occipital 6 cm×7 cm, feu temporal 10 cm×7 cm et feu bregmatique 10 cm×6 cm

Dans ces conditions le volume cible est de 420 ml

La dose tumorale est identique a celle administree par radiotherapie conventionnelle, mais avec un etalement plus court reparti sur huit a neuf semaines, soit 110 rad gamma par seance et par jour

Resultats

Survie therapeutique globale des glioblastomes (Fig 6a)

A un an le pourcentage des survies n est que de 42 % Plus que la moitie des malades sont decedes dans la premiere annee

SUMMARY

The results of postoperative radiotherapy in 87 cases of glioblastoma multiforme were analysed according to well defined anatomical criteria A comparison was made of results obtained by conventional radiotherapy and gamma therapy Two factors are of prime importance in the survival of the patients the optimal dose should be in the range 5 000 to 7 000 rad superior or inferior doses compromising the results the volume irradiated should comprise the whole cerebral hemisphere the tumour site because of the infiltrative nature of cerebral tumours

ZUSAMMENFASSUNG

Die Ergebnisse bei der post operativen Strahlenbehandlung in 87 Fallen von Glioblastom multiforme wurden gemass genau definierten anatomischen Kriterien ausgewertet und ein Vergleich zwischen konventioneller Radiotherapie und Gammatherapie wurde vorgenommen Die optimale Dosis liegt zwischen 5 000 und 7 000 rad hohere oder niedrigere Dosen kompromittieren di Resultate Das Bestrahlungsvolumen soll aufgrund der Neigung zur Infiltration der Gehirntumoren die ganze Grosshirnhamisphere das Tumorfeld umfassen

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A deux ans, memes resultats, entre 5 000 et 7 000 rad, gain de 25 % par rapport a une dose inferieure a 5 000 rad/tumeur. Au dessus de 7 000 rad, tous les malades sont decedes.

On peut donc conclure que la dose optimale se situe entre 5 000 et 7 000 rad/tumeur et que, si les resultats sont moins bons, au dessous de 5 000 rad ils sont franchement mauvais au dessus de 7 000 rad.

Survie therapeutique en fonction du volume irradie (Fig 7b)

A un an, la survie est deux fois plus elevee apres irradiation totale de l'hemisphere (57 %) qu'apres irradiation partielle (28 %).

A deux ans, les resultats sont identiques, 15 % contre 8 % en irradiation partielle.

Conclusions

Il ressort de notre etude que la survie exceptionnellement courte des glioblastomes, puisqu'elle ne depasse pas trois ans dans l'ensemble, peut etre influencee par plusieurs facteurs qui meritent d'etre retenus car l'action therapeutique des radiations peut être fortement compromise s'ils ne sont pas respectes.

Nature des radiations. Comme nous l'avions deja observe dans nos travaux precedents il semble que la radiotherapie conventionnelle donne des survies plus longues que la gammatherapie.

La dose optimum se situe entre 5 000 et 7 000 rad tumeur. Au dessous de 5 000 rad, les resultats sont moins satisfaisants et au dessus de 7 000 rad ils sont franchement mauvais.

Le volume cible irradie. L'irradiation de la totalite de l'hemisphere tumoral est une necessite imperieuse qui tient a la nature infiltrante tres particuliere des glioblastomes qui poussent des prolongements tumoraux en tissu apparemment sain et qui constitueront le siege des recidives.

RÉSUMÉ

Les auteurs ont étudié les resultats du traitement radiothérapique post operatoire de 87 cas de glioblastomes multiformes suivant des criteres anatomiques bien définis. Ils ont comparé les résultats obtenus par radiothérapie conventionnelle et par gammathérapie. Deux facteurs ont une importance majeure dans la survie thérapeutique des malades traité : la dose optimum se situe entre 5 000 et 7 000 rad, des doses superieures ou inferieures compromettent le résultat ; le volume cible doit comporter l'irradiation de la totalite de l'hémisphere cérebral siège de la tumeur du fait du caractere tres infiltrant des tumeurs cerebrales.

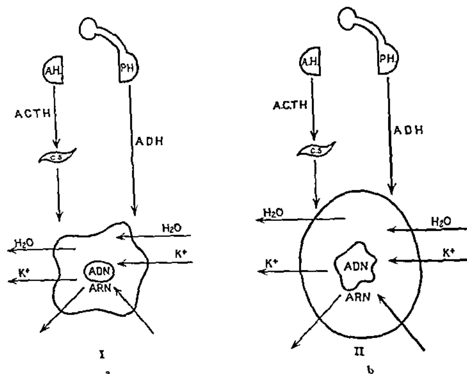


Fig 1 a) Schématisation de la regulation centrale du metabolisme cellulaire au point de vue hormonal en partie d apres des travaux personnels (BERNARD-WEIL 1965 1968) b) Facteurs hormonaux de l œdeme cerebral l hypersecretion d ADH joue un role aggravant AH—ante hypophyse ADH—hormone antidiuretique CS—cortico-surrenales PH—post hypophyse

liennes qui expulsent l eau et le potassium de la cellule et d autre part l hormone antidiuretique ou vasopressine (ADH) qui realise l effet inverse (Fig 1a)

Il est donc certain que l ADH en exces joue un role aggravant dans la genese ou tout au moins dans l aggravation de l œdeme cerebral Precisement nous avons demontre que les porteurs de glioblastomes cerebraux avaient un taux de secretion d ADH exagere Ce phenomene est en rapport avec la compression de l hypothalamus par la tumeur et a son tour aggrave l œdeme cerebral C est une sorte de cercle vicieux D autre part cette hypersecretion d ADH est liee a la nature cancereuse elle meme de la tumeur car en comparant une serie de meningiomes et une serie de glioblastomes ou de metastases nous avons constate un abaissement de la clearance de l eau libre qui temoigne de l hypersecretion d ADH significativement plus prononcee chez les porteurs de tumeurs malignes cérebrales (BERNARD WEIL et coll 1967) Le resultat de ce desequilibre hormonal c est un

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TRAITEMENT COMPLÉMENTAIRE ENDOCRINIEN DES TUMEURS CÉRÉBRALES

par

E. BERNARD WEIL

Vous devez vous demander ce que vient faire un neuroendocrinologiste dans une Table Ronde consacrée à la thérapeutique des glioblastomes. En quelques minutes, je vais essayer de vous faire soupçonner l'importance de cette discipline dans le cadre de la neurochirurgie, de la radiologie, voire de la cancérologie.

Le risque d'une aggravation de l'œdème cérébral au cours de la radiothérapie des gliomes est considéré par vous comme sérieux et vous souhaiteriez disposer d'une arme efficace contre la survenue de tels accidents. Or le traitement anti-œdémateux dont les effets sont à la fois les plus puissants et prolongés est constitué, à notre avis, celui du Professeur David et le nôtre propre, par une association d'hormones cortico-surrénaliennes et post-hypophysaires.

Il est vrai que certains d'entre vous utilisent déjà des cortico-stéroïdes type prednisone ou bétaméthasone, ou encore de l'ACTH, comme nous l'avions déjà recommandé il y a plus de 6 ans. Mais ce type de traitement nous paraît insuffisant, incomplet. Cependant l'explication d'une efficacité éventuelle des hormones cortico-surrénaliennes isolées peut être donnée par la schématisation suivante.

L'œdème cérébral est, comme vous le savez, un œdème principalement cellulaire et il existe deux influences endocriniennes susceptibles de modifier la teneur en eau et en ion potassium de la cellule. D'un côté les hormones cortico-surréna-



Fig 3 Aspects successifs de l artériographie carotidienne de face chez un porteur d astrocytome mal n temporal gauche avant l intervention sous l effet du traitement hormonal (six semaines entre les deux clichés)

La premiere technique utilise un extrait post hypophysaire total comportant de l ocytocine et de la vasopressine qui par un mecanisme de « feed back » semble pouvoir fixer le taux de secretion endogene d ADH à un certain niveau (post hypophyse polyvidone Choay® une unite le premier jour, *puis augmentation* d une unite par jour jusqu a 7—8 unites puis posologie *decroissante*) Cette therapeutique seule serait evidemment aggravante mais en l a..o tant a des do es as ez elevees d ACTH 75 unites en *perfusion par 24 heures* nous allons provoquer une diminution de l œdeme cerebral (BERNARD WEIL et coll 1966)

Une autre technique utilise de l *ocytocine seule qui* par un mecanisme egalement central parait pouvoir freiner un peu la secretion d ADH (Syntocinon® a 2 unites en 2 *ml* 0 8 *unite* en perfusion continue de 24 heures le premier jour, augmentation de 0 8 unite par *jour jusqu a* 4—4 8 unites, puis posologie decroissante) Dans ces conditions il est permis d utiliser des doses d ACTH plus faibles de l ordre de 20—30 unites par 24 heures (BERNARD WEIL et coll 1967)

Mais c est surtout de la premiere therapeutique que nous avons la pratique la plus etendue Nous n avons pas une experience personnelle et systematique de l association de cette therapeutique avec la *radiotherapie* Par contre notre service et beaucoup d autres cliniques neuro-chirurgicales y ont recours d une

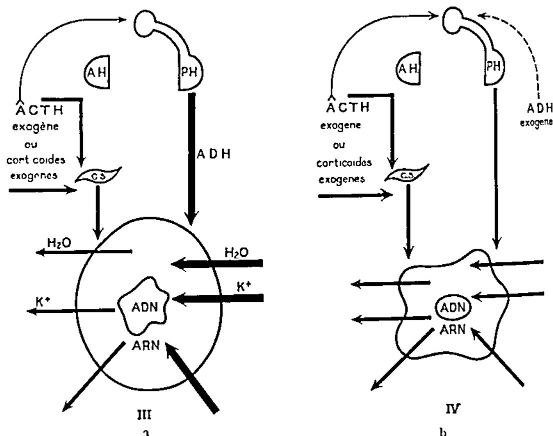


Fig 2 a) Le traitement par les corticoïdes et l'ACTH paraît indiqué en cas d'œdème cérébral mais il risque de déclencher une majoration de l'hypersécrétion d'ADH L'épaisseur des flèches est proportionnelle à l'activité endocrinienne b) L'association d'extrait post hypophysaire aggrave la surcharge hormonale en ADH mais la stabilise L'apport à doses convenables d'hormones cortico surrénaliennes entraîne alors une action favorable sur l'œdème cérébral

gonflement cellulaire car il y a plus d'eau qui entre dans la cellule que d'eau qui en sort (Fig 1b)

La thérapeutique par les cortico-stéroïdes ou par l'ACTH est en principe valable puisqu'elle entraîne une sortie d'eau et d'ion potassium Mais, dans de très nombreux cas, cette thérapeutique, théoriquement justifiée, va déclencher ce que nous avons appelé la réaction neuro post hypophysaire à la surcharge en cortico stéroïdes, si bien que s'il sort plus d'eau et d'ion potassium il va en rentrer encore davantage, et l'effet favorable de l'ACTH de la bétaméthasone ou de la prednisone va être annulé l'œdème cérébral persiste ou réapparaît (Fig 2a)

C'est pourquoi nous avons proposé une association d'hormones cortico surrénaliennes et post hypophysaires ces dernières étant seulement là pour empêcher la majoration compensatrice de l'hyper sécrétion d'ADH (Fig 2b)



a



b



c

Fig 5 a) Arteriographie carotidienne de face droite chez un porteur d oligodendrogliome frontal droit avant l intervention b) Arteriographie six semaines apres l intervention c) Arteriographie 15 jours plus tard le traitement hormonal ayant ete mis en route immediatement apres (b)

persiste On applique pendant 10 jours le traitement hormonal que je vous ai decrit Le malade sort du coma son hemiplegie regresse et l arteriographie montre une diminution des anomalies precedemment observees

Nous pensons donc qu une telle therapeutique vous faciliterait grandement la

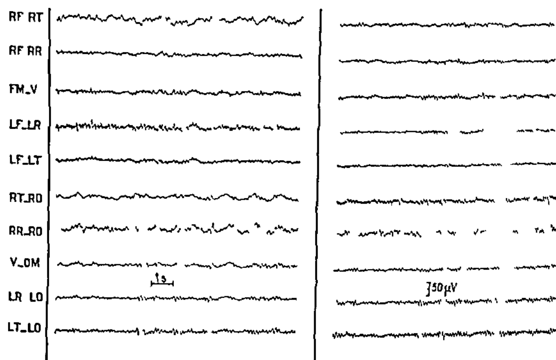


Fig 4 Variations du tracé électroencéphalographique chez un porteur de glioblastome fronto-temporal droit avant l'intervention sous l'effet du traitement hormonal (sept jours entre les deux tracés)

manière intensive à titre pré et post opératoire En voici quelques exemples illustrés par des examens complémentaires réalisés dans le Service du Professeur Fischgold

Une malade de 42 ans (Fig 3), *aphasique et hémiplégique* avec une image de processus occupant l'espace temporal gauche, s'améliore au bout d'un mois de traitement hormonal Vous voyez l'engagement sous la faux ainsi que la déviation de la péri calleuse Voici un mois après alors que la malade est ambulatoire *et n'a plus de syndrôme d'hypertension intracrânienne* l'engagement sous la faux a diminué et la déviation de la péri calleuse a également regressé La malade a été opéré dans les meilleures conditions pour un astrocytome dégénéré de la pointe du lobe temporal

Un malade de 47 ans (Fig 4) arrive avec des troubles de la conscience et une hémiplégie gauche Le traitement hormonal entraîne une amélioration clinique et électroencéphalographique avant l'exérèse de ce glioblastome fronto temporal droit dans les meilleures conditions opératoires

Le dernier malade (Fig 5), âgé de 58 ans est opéré pour un oligo dendrogliome frontal droit Quatre semaines après l'intervention ce malade est hémiplégique et comateux et une déviation importante des artères de la ligne médiane

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radiothérapie des gliomes cérébraux en autorisant une plus rapide délivrance des doses fixées et en permettant les innovations auparavant interdites par le risque majeur d'œdème cérébral.

RÉSUMÉ

L'utilisation d'un traitement hormonal anti-œdémateux cérébral est envisagé dans le cadre de la thérapeutique des gliomes intra-crâniens. L'auteur rappelle les bases physio-pathologiques d'un tel traitement. L'hyperhydratation cellulaire de l'œdème cérébral est endocrinologiquement liée à une sécrétion d'hormone antidiurétique exagérée par rapport à celle des hormones antagonistes cortico-surrénaliennes. Il est donc indiqué de prescrire une corticothérapie, mais associée à l'administration d'un extrait post-hypophysaire afin de mettre la neuro-hypophyse hors circuit et de l'empêcher d'annuler par son hyperfonctionnement accru les effets théoriquement favorables des corticoïdes (ou de l'ACTH). Des exemples sont donnés des améliorations obtenues dans le cas de gliomes traités de cette manière au stade pré-opératoire (par comparaison d'artériographies et d'électroencéphalographies successives notamment). Il paraît en conséquence raisonnable d'associer une thérapeutique de ce genre lors de la radiothérapie des gliomes cérébraux.

SUMMARY

The use of anti-oedematous cerebral hormones in connection with therapy of intracranial gliomas is discussed. The author recalls the physio-pathologic basis for such treatment: cellular hyperhydration of the cerebral oedema is connected with excessive secretion of the antidiuretic hormone in relation to the level of the antagonistic adreno-cortical hormones. The prescription of corticotherapy is thus indicated with simultaneous administration, however, of a post-hypophyseal extract in order to eliminate the neurohypophysis from the circuit and prevent it from counteracting by its hyperfunctioning the expected favourable effects of the corticoids. Examples are given of improvements obtained by such pre-operative treatment of gliomas as shown by arteriography and electroencephalography. It appears logical to apply this type of therapy together with radiotherapy in the treatment of cerebral glioma.

ZUSAMMENFASSUNG

Die Verabreichung von anti-odematosen cerebralen Hormonen bei der Therapie der intrakraniellen Gliome wird besprochen. Es wird an die physio-pathologischen Grundlagen dieser Behandlung erinnert: die Hyperhydratation der Zellen ist endokrinologisch mit einer übermässigen Sekretion des antidiuretischen Hormones im Verhältnis zur Sekretion des antagonistischen cortico-adrenalen Hormones verbunden. Corticotherapie mit Verabreichung eines post-pituitaren Extraktes wird empfohlen, um die Neurohypophyse ausser Funktion zu setzen und zu verhindern, dass die theoretisch vorteilhafte Wirkung der Corticoide herabgesetzt wird. Es werden einige Beispiele angeführt, in denen Besserung bei solcher pre-operativer Behandlung erreicht wurde. Es scheint deshalb angebracht diese Behandlung zusammen mit Bestrahlung der cerebralen Gliome einzusetzten.

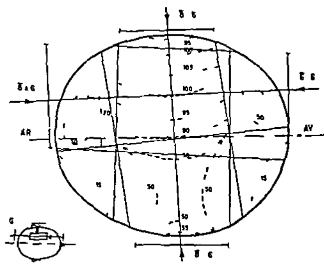


Fig 1 Irradiation d une tumeur parietale au 220 kV CDA 1 5 mm Cu au moyen de 5 champs fixes DSP 60 cm

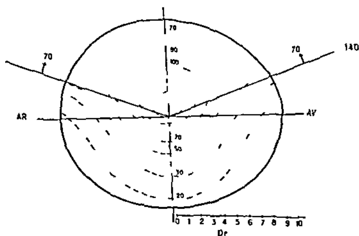


Fig 2 Irradiation pendulaire laterale d une tumeur parietale au 250 kV CDA 1 75 mm Cu L isodose de reference est l isodose 90

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RADIOTHERAPIE DES GLIOBLASTOMES DE L'ADULTE ET DE L'ENFANT

par

M SCHLIENGER

Glioblastomes de l adulte — Sur une periode de 10 ans, de 1956 au 1er Juillet 1966, nous avons irradie 72 cas d astrocytomes grade IV, ou glioblastomes *multiformes de l adulte*

La majorite de ces malades ont ete operes par le docteur J P Constans En dehors de 3 malades dont l intervention n avait consiste qu en une simple de compression avec biopsie, tous les autres avaient subi soit une exerese macro scopiquement complete, soit une exerese subtotale ou partielle

Ces 72 cas de glioblastomes representent 50 % environ des gliomes de l adulte irradies a l I G R , pendant la même periode (148 cas)

De ces 72 malades 59 ont ete irradies systematiquement apres l intervention, ce traitement a ete entrepris entre 25 et 60 jours apres l intervention (30 jours en moyenne)

Un nombre plus faible de malades (13) a ete irradie au stade de recidive clinique (*180 jours en moyenne*) apres l exerese *chirurgicale* La repartition suivant l age au moment du traitement est la suivante

de 21 a 30 ans	2 cas
de 31 a 40 ans	10 cas
de 41 a 50 ans	16 cas
de 51 a 60 ans	29 cas
de 61 a 70 ans	13 cas
au dela de 71 ans	2 cas

deux champs etaient irradies le premier jour les trois autres l etant le 2eme jour et ainsi de suite

La dose hebdomadaire etait de l ordre de 800 a 900 rad et la duree totale d environ 6 a 8 semaines Ce type d irradiation (5 jours sur 7) fut conserve jusqu au fin de 1963 en irradiation pendulaire

Depuis 1964 nous avons irradie les malades a raison de 3 seances par semaine (3×330 rad par semaine) jusqu a une dose totale de 5 500 rad delivres en 6 semaines Ces modifications avaient comme raison pratique la reduction du nombre de mises en place sous une machine surchargee Nous avons evalue a 10 % l augmentation de l efficacite biologique due au passage de 5 seances par semaine a 3 seances par semaine Ainsi 5 500 rad devenaient l equivalent biologique de 6 000 rad delivres pendant la meme duree de 6 semaines a raison de 5 seances par semaine

Actuellement en dehors des cas s accompagnant d une hypertension intracranienne importance nous avons l habitude de debuter le traitement a la dose de 330 rad par séance L utilisation du traitement neuro-hormonal de B WEIL et DAVID commence avant le traitement et poursuivi durant toute sa duree a grandement facilite la conduite des traitements dans la quasi totalite des cas Ainsi les irradiations effectuees depuis plusieurs annees sont-elles en general plus conformes au plan de traitement qu elles ne l etaient avant l introduction de ce traitement medical

Resultats et Discussion

Les resultats sont donnes par le Tableau 1

La survie est comptee a partir de l intervention chirurgicale Ces resultats sont semblables a ceux fournis par TAVERAS (1962), UIHLEIN et coll (1966) mais inferieurs a ceux de BOUCHARD (1966)

Nous ne disposons pas d une serie chirurgicale parallèle permettant de faire une etude comparative de la longeur de survie apres l intervention seule statistiquement valable Neanmoins plusieurs travaux recents on mis l accent sur l allongement de la survie obtenue par une radiotherapie complémentaire de la chirurgie (UIHLEIN et coll 1966)

I Volume a irradier et dose

Le volume dans lequel la dose de radiation sera delivree est determine au cours d une consultation commune avec le neuro-chirurgien (Dr J P Constans) et l interniste charge de la surveillance medicale du traitement (Mme le docteur J Roujeau)

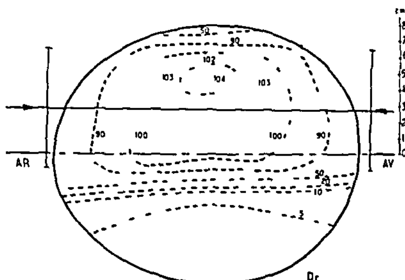


Fig. 3. Irradiation d'une tumeur pariétale aux photons de 24 MV du bétatron. Champs antérieur et postérieur 8 cm × 8 cm. DSP 100 cm. Isodose de référence 100 %.

L'étude de la répartition topographique montre que sur 61 cas d'atteinte d'un seul lobe, le lobe frontal était intéressé dans 25 cas, le lobe temporal dans 22 cas. Les 14 cas restant se répartissaient entre le lobe pariétal (9 fois), occipital (3 *fois*), *tumeurs centrales* (2 *cas*).

Une atteinte de deux lobes ou plus a été retrouvée dans 11 cas.

Mode d'irradiation

Les modalités de l'irradiation ont au cours de ces 10 années subi des changements dépendant surtout de l'appareillage disponible.

De 1956 à 1961, l'irradiation a été effectuée par rayons de 200 kV (CDA 1,75 mm Cu) au moyen de 4 à 5 portes d'entrée.

De 1962 à la fin de 1965, nous avons utilisé l'irradiation en pendulaire à l'aide d'un appareil de 250 kV à tension constante (CDA 1,75 mm Cu).

Depuis le début de 1966, les malades sont traités aux photons de 20 MV du bétatron.

Les dimensions des portes d'entrée et la répartition de la dose sont explicites dans les *Figs* 1, 2, et 3 *concernant une tumeur pariétale*.

Si les doses totales n'ont que peu varié (5 000 à 6 000 rad) l'étalement et le fractionnement ont subi des modifications.

L'irradiation par champs fixes se faisait à raison de 5 séances par semaine

S Kramer (CONCANNON et coll 1960) au cours de cette reunion nous a rappele es travaux et montre des exemples d extension tumorale insoupçonnee

Notre materiel d autopsie comporte 16 cas sur 72 malades traites Nous n avons pas retrouve dans cette petite serie d extension du type precedent Nous n avons pas pu a posteriori reconstituer de façon valable les relations entre la dose delivree dans le volume cible et la dose dans certaines zones du voisinage ou a distance de celui-ci comme M Lindgren l a fait (BERG & LINDGREN 1958 LINDGREN 1958)

Il est a noter que 6 des autopsies concernent des malades decedes en cours de traitement apres des doses inferieures a 3 000 rad en 4 semaines Ces reserves etant faites la confrontation des isodoses et des cliches de centrage et donnees anatomiques ne nous a pas montre de volume cible irradie de façon incomplete sauf dans quelques cas d irradiation pendulaire ou l angle de balayage etait trop ferme Certaines zones de la peripherie du volume cible n ont reçu ainsi que 80 % de la dose tumorale

Il e t difficile de comparer d une serie à une autre les survies en fonction de la dose delivree La selection des malades a irradier releve de trop de variables Le nombre de cas ne terminant pas l irradiation donne une idee des indications du traitement et du materiel frequemment pejoratif retenu Ainsi UIHLEIN et coll (1966) trouvent que la survie est plus longue dans la serie ayant reçu plus de 3 500 rad Ils ne precisent pas s il s agit de malades qui comme dans notre s rie ont reçu un traitement incomplet en raison de l aggravation rapide de leur etat en cours d irradiation

À titre d information nous presentons ici les taux de survie compares des malades ayant ou non termine leur traitement Nous avons inclus les astrocytomes grade III (15 cas) Les taux de survie a 6 mois (60 %) a un an (26 %) sont assez voisins de ceux des glioblastomes A 2 ans on remarque que ce taux est de 23 % a 3 ans de 16 % et a 4 ans de 0 % (Tableau 2)

2 *Fractionnement de la dose*

En 1954 nous avons commence a irradier un certain nombre de localisations suivant un protocole nouveau d irradiation concentree en deux series (DUTREIX et coll 1967) 1ere serie 1 700 rad en 2 seances et 3 jours (equivalent a 3 000 rad en 3—4 semaines), repos 19 jours et 2eme serie 2 700 rad en 9 seances et 21 jours

L ensemble de cette irradiation est l equivalent de 6 000 rad en 6 semaines a raison de 5 s ances hebdomadaires

A cette epoque nous recevions d hopitaux peripheriques des malades porteurs

Tableau 1

Glioblastomes de l'adulte (1956—30/6 1966) (72 cas) — Irradiation après chirurgie — Les chiffres entre parenthèses indiquent le nombre de malades ayant le recul indiqué

Survie à	Taux de survie
6 mois	67 % (72)
1 an	32 % (72)
2 ans	7,4 % (67)
3 ans	3,0 % (60)
4 ans	2,1 % (46)
5 ans	2,5 % (39)
6 ans	4,5 % (22)
7 ans et plus	0 % (11)

Tableau 2

Glioblastomes (72 cas) et astrocytomes grade III de l'adulte (15 cas) 1956—30/6 1966) — Taux de survie comparés des cas ayant subi une irradiation complète et des cas n'ayant pas terminé leur traitement — Les chiffres entre parenthèses indiquent le nombre de malades ayant le recul indiqué

Survie à	Irradiation complète	Irradiation inachevée
6 mois	76 % (72)	13,3 % (15)
1 an	37,5 % (72)	0 % (15)
2 ans	12,2 % (66)	0 % (14)
3 ans	6,6 % (60)	0 % (12)
4 ans	2,2 % (45)	0 % (12)
5 ans	2,7 % (37)	0 % (10)
6 ans	4,3 % (23)	0 % (2)
7 ans et plus	0 % (11)	0 (2)

En se fondant sur les données pré-opératoires (artériographie, encéphalographie gazeuse, gammagraphie dans certains cas) et sur les constatations opératoires, on détermine le volume cible. En général, il dépasse de 3 cm dans les 3 dimensions les limites présumées de la tumeur.

Il est admis actuellement que le glioblastome est une maladie d'organe toujours plus étendu homo- et controlatéralement qu'on peut le soupçonner (JONES 1963).

Il semble donc nécessaire d'irradier à des doses importantes la majeure partie de l'encéphale ou tout au moins d'un hémisphère.

Lorsque l'on emploie la technique à champs multiples au 200 kV (LECRE et *coll.* 1966), dans l'exemple de Fig. 1, on s'aperçoit que la plus grande partie de l'hémisphère opposé reçoit une dose de l'ordre de 2 500 à 3 000 rad pendant les 6 à 8 semaines du traitement.

Dans le cas illustré dans Fig. 2, l'irradiation controlatérale est nettement moins importante. Enfin, le traitement effectué selon les modalités de Fig. 3 n'intéresse pratiquement que l'hémi-encéphale tumoral, compte tenu d'une certaine marge de sécurité constituée par le débord d'un centimètre des portes d'entrée du côté de l'hémisphère controlatéral. La confrontation, à l'examen anatomique de l'étendue de la tumeur et du volume cible a permis à CONCANNON et coll. (1960), à TODD (1963) de recommander une irradiation de la majeure partie de l'encéphale à des doses voisines de la dose tumorale.

qu en arriere sur le pli courbe et le lobe parietal attenant Pas d œdeme ni d hemorragie »

On sait d ailleurs les difficultes d interpretation des phenomenes necrotiques decouverts a l examen d un encephale porteur d un glioblastome en evolution apres une intervention chirurgicale et une irradiation Sur les 66 malades irradiees selon les modalites habituelles nous avons 15 autopsies Six de ces examens anatomiques concernaient des malades ayant reçu de faibles doses (inferieures a 3 000 rad) car la mort etait survenue au cours du traitement Dans l ensemble il n a pas ete signale de necrose a distance des foyers tumoraux Comme nous l avons dit plus haut malheureusement les correlations entre les lesions necrotiques observees et les volumes irradies n ont pas ete etablies exactement Nous ne pouvons donc utiliser les donnees de Martin Lindgren concernant les limites de tolerance du tissu nerveux

3 *Moment de l irradiation*

Bien des auteurs admettent a l heure actuelle que l irradiation postoperatoire est un complement necessaire de l exerese chirurgicale entreprise dans le mois qui suit l intervention Ainsi est definie l irradiation post operatoire precoce de principe que l exerese soit macroscopiquement complete ou non A l oppose certains malades sont irradies en fonction de la reprise des signes d hypertension intracranienne ou de l aggravation des signes neurologiques Il s agit d une irradiation tardive de necessite effectuee dans des delais variables en fonction des caracteristiques de la tumeur Il nous a semble interessant de confronter les resultats de ces deux groupes et d essayer ainsi d eclairer le probleme du moment de l irradiation

Il y a 59 cas dans notre serie qui repondent a la premiere definition Ils ont ete irradies 30 jours en moyenne apres l intervention et onze de ces malades ont reçu une dose inferieure a 4 000 rad (traitements incomplets) La duree de la survie moyenne est de 2 mois apres l intervention chirurgicale la survie mediane de 1 5 mois Il s agit la evidemment d un groupe de malades dont l etat s est aggrave progressivement depuis l intervention que certains pourraient classer dans les morts post-operatoires

Le groupe des malades ayant deja reçu une irradiation complete comporte 48 cas Les survies (comptees a partir de l intervention chirurgicale) sont survie moyenne 12 mois survie mediane 8 5 mois

Il est interessant de comparer ce dernier groupe avec la serie de 13 cas irradies en moyenne 180 jours apres l intervention alors qu il existait une recidive clinique evolutive

Tableau 3

Résumé de l'histoire clinique dans cinq cas de glioblastomes de l'adulte (1965) — Irradiation concentrée en deux séries 1ère série 1 700 rad/2 séances/3 jours repos 19 jours 2ème série 2 700 rad/9 séances/21 jours

No Dossier I G R	Intervalle chirurgie — irradiation	Survie après irradiation	Mode de traitement	
			Energie	Traitement
65 0059	25 jours	7 mois	250 kV	Complet
65 0780	* 6 mois	6 mois**	250 kV	Complet
65 1163	* 5 1/2 mois	9 1/2 mois	250 kV	Complet
65 2149	* 9 1/2 mois	7 1/2 mois **	250 kV	Complet
65 2346	* 4 mois	10 jours	250 kV	Inachevé (1ère série)

* Tumeur en récidive clinique
** Autopsie

de glioblastomes en récidive clinique, en très mauvais état, comateux le plus souvent Nous avons essayé de les irradier suivant le schéma précédent

Il nous avait semblé licite de traiter ainsi ces malades au dessus de toute ressource thérapeutique, sachant que nous prenions le risque de poussées hypertensives intracrâniennes Celles-ci se sont effectivement produites après la 1ère et la 2ème séances, mais le traitement médical poursuivi a pu éviter une issue fatale, sauf dans un cas mort le 10ème jour après l'irradiation

Le Tableau 3 résume l'histoire de ces cinq cas

Il est intéressant de constater que quatre sur cinq de ces malades ont pu recevoir une irradiation complète et que des survies valables ont été obtenus alors qu'ils paraissaient voués en apparence à une évolution terminale rapide Nous avons irradié selon ce schéma deux astrocytomes grade III qui n'ont pu recevoir que la 1ère série et sont morts un mois après l'irradiation Dans les deux cas il s'agissait de récidive rapide après chirurgie effectuée 4 mois auparavant

Nous utilisons encore ce mode d'irradiation lorsque le contexte clinique nous y autorise

Le danger de nécrose cérébrale est évidemment le problème majeur et l'écueil de cette technique Nous n'avons que deux autopsies parmi ces six cas

Cas 65 0780 — « Tumeur envahissant pratiquement tout l'hémisphère gauche les noyaux gris centraux » (on ne mentionne pas de radionécrose)

Cas 65 2149 — « Masse blanchâtre, dure située dans le lobe temporal gauche siégeant dans la partie moyenne de T2 empiétant largement sur T1 et T3 ainsi

Tableau 5

Dix-huit cas de glioblastomes de l'enfant vérifiés histologiquement — État au 1er juillet 1967

	Cas	Irradiation incomplète	Vivants au juillet 1967	Année du décès*				
				0 à 6 mois	7 à 12 mois	13 à 24 mois	25 à 36 mois	37 à 48 mois
Tumeurs hémisphériques	8	2	0	3	1	2	1	1
Tumeurs profondes	3		0	1	2	—	—	—
Tronc cérébral	2	1	0	1	1	—	—	—
Cervelet (1 cas irradié sans chirurgie préalable)	5	1	0	1	4	—	—	—
Total	18	4***	0	6	8	2	1	1
				14				

* Survie comptée à partir de l'intervention ou du début de la radiothérapie (chez les malades non opérés)
** Trois fois — diagnostic histologique établi à l'autopsie (pas d'intervention chirurgicale)
*** Traitements incomplets 4 décès dans un délai < 15 jours après le début de l'irradiation

rait se faire d'ailleurs après une deuxième intervention. Le malade pourrait mener dans ce cas pendant quelques mois une vie aussi normale que possible. Dans l'affirmative, l'on est conduit à une certaine souplesse dans les indications et à adapter celles-ci à chaque cas.

A l'argument radiobiologique vérifié sur d'autres tumeurs nous enseignant qu'il vaut mieux irradier lorsque le nombre de cellules tumorales est au minimum, c'est-à-*dire dans* le mois suivant l'intervention, l'on peut répondre que le glioblastome ne semble pas être radiocurable pour des doses respectant les limites de tolérance du tissu nerveux.

Il faut envisager aussi les conditions du traitement : il est en général plus facile de mener à son *terme une* irradiation post-opératoire précoce car les malades sont dans l'ensemble en meilleur état, plus coopérants qu'au stade de récidive. A ce moment de leur *évolution ils* sont parfois une lourde charge hospitalière par l'importance des soins qu'ils requièrent.

En dernière analyse, il n'apparaît pas illogique d'attendre la récidive pour effectuer l'irradiation plutôt que d'épuiser d'emblée les possibilités de la radiothérapie en effectuant l'irradiation post-opératoire précoce. Il est difficile de démontrer sur une localisation ayant un si mauvais pronostic la supériorité de l'une ou de l'autre méthode. En définitive, l'attitude thérapeutique dépend de

Tableau 4

Glioblastomes de l'adulte (1956—30/6 1966) — Survie moyenne et survie médiane en fonction du moment de l'irradiation post-opératoire, soit précoce de principe, soit tardive pour récidive

	Nombre de cas	Survie moyenne		Survie médiane	
		Traitement complet	Traitement incomplet	Traitement complet	Traitement incomplet
Irradiation post-opératoire de principe précoce (délai moyen entre chirurgie et irradiation = 30 jours)	59	12 mois (48 cas)	2 mois (11 cas)	8 1/2 mois (48 cas)	1 1/2 mois (11 cas)
Irradiation tardive de nécessité (délai moyen entre chirurgie et irradiation = 180 jours)	13	17 mois (9 cas)	4 mois (4 cas)	18 mois (9 cas)	4 mois (4 cas)

Il s'agit de 13 cas dont les survies moyennes et médianes sont de 13 mois (9 sur 13 seulement ont reçu une irradiation complète).

Il est certain que cette comparaison n'a qu'une valeur relative, car il s'agit de groupes très inégaux en nombre, et disparates, le second constitue une sélection de malades ayant vécu plus de quatre mois (intervalle le plus faible entre la chirurgie et les irradiations dans ce groupe). Il faut remarquer que 4 malades sur 13 ont reçu une irradiation incomplète, ce qui est proportionnellement plus important que dans le premier groupe de 59 malades (dont 11 cas n'ont pas terminé leur traitement). De nombreux autres points pourraient être discutés mais aboutiraient à comparer de très petits groupes : chirurgie complète (5/13 et 20/48), atteinte ou non des noyaux gris centraux — localisation lobaire ou bilobaire. *Il y a une sélection spontanée des tumeurs moins évolutives dans le 2ème groupe*, mais la survie moyenne des malades appartenant au premier groupe et ayant vécu plus de six mois après la chirurgie est de 11 mois.

En résumé, toutes ces réserves étant faites et compte tenu du peu de différence entre les deux groupes, il ne semble pas exister d'argument convaincant plaidant en faveur de l'irradiation précoce systématique, ou en faveur de l'irradiation tardive.

Du fait de la médiocrité des résultats, place doit être faite dans la discussion à des arguments qualitatifs. N'est-il pas légitime de proposer à un malade venant de subir une intervention grave, mais sans séquelle fonctionnelle majeure et pouvant être suivi régulièrement, une simple surveillance réservant ainsi l'irradiation pour le traitement de la récidive quasi inéluctable. L'irradiation pour

SUMMARY

Seventy two adults with glioblastoma, in 69 of whom the tumour had been more or less completely extirpated, received roentgen treatment in the period between 1956 to July 1966. The rates of survival were: 6 months in 67 %, a year in 32 %, 2 years in 7.4 %, 3 years in 3 % and 4 years in 2.1 %. Eighteen children with histologically verified glioblastoma received roentgen treatment in the period between 1952 to July 1966. Fourteen of these patients died during the first year, two during the second, and one patient during each of the third and fourth years. In view of these poor results and following a discussion of irradiation volumes and dosage it is suggested that the patients may suffer less strain if irradiation after operation is given only in cases of recurrence.

ZUSAMMENFASSUNG

Zwischen 1956 und Juli 1966 wurden 72 Erwachsene mit Glioblastom, in 69 von denen der Tumor mehr oder weniger komplett exstirpiert war, mit Röntgenbestrahlung behandelt. Die Überlebensraten waren: 6 Monate in 67 %, 1 Jahr in 32 %, 2 Jahre in 7.4 %, 3 Jahre in 3 % und 4 Jahre in 2.1 %. In den Jahren 1952 bis Juli 1966 wurden 18 Kinder mit histologisch verifiziertem Glioblastom mit Röntgenbestrahlung behandelt. Vierzehn von diesen Patienten starben im ersten Jahr, zwei während des zweiten Jahres und je ein Patient im dritten und vierten Jahr. Mit Hinsicht auf diese unbefriedigenden Resultate und nach einer Diskussion geeigneter Bestrahlungsvolumen und Dosierung wird angenommen, dass man vielleicht den Patienten weniger Leiden verursachen möchte, wenn nur die postoperativen Rezidivfällen bestrahlt werden.

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l'intention finale, visant soit à rechercher à tout prix une stérilisation que l'expérience montre illusoire, soit à assurer au malade la survie la plus confortable physiquement et moralement.

Glioblastomes de l'enfant. — Nous présentons ici (Tableau 5) les résultats concernant les 18 glioblastomes de l'enfant irradiés à l'I.G.R. de 1952 au 1er juillet 1966. La technique d'irradiation et les doses ont été les mêmes que chez l'adulte. Les malades opérés ont été irradiés dans des délais allant de 15 jours à 33 jours après l'intervention, sauf un seul cas (72 jours).

Quatre malades sur 18 n'ont subi qu'un traitement incomplet et sont morts dans des délais inférieurs à 15 jours : une tumeur du tronc (450 rad/5 séances/une semaine), une tumeur du cervelet (600 rad/5 séances/9 jours), deux tumeurs hémisphériques (500 rad/5 séances/5 jours) et (300 rad/3 séances/5 jours). Les trois premiers de ces cas ont été traités en 1952 et 1957.

Les résultats apparaissent aussi médiocres que chez l'adulte.

Conclusion. — La médiocrité des résultats incite à rechercher l'association d'autres moyens à l'irradiation post opératoire, comme oxygène hyperbare (CHANG), et injection intracarotidienne de BudR (DOGGETT). L'irradiation sous hypothermie paraît dangereuse (BLOOR et coll. 1962).

Enfin, il faudrait peut-être réexplorer le problème du fractionnement et essayer d'adapter l'irradiation à la vitesse de croissance de la tumeur. Notre tentative d'irradiation concentrée en deux séries est un pas dans cette direction.

Remerciement

Nous remercions vivement Mme le Docteur Vogt Hoerner pour avoir revu les coupes histologique des glioblastomes de l'enfant.

RÉSUMÉ

De 1956 à Juillet 1966, 72 cas de glioblastomes de l'adulte ont été irradiés, dont 69 malades avaient subi une exérèse plus ou moins complète. Les taux de survie sont à 6 mois 67 %, à un an 32 %, à 2 ans 7,4 %, à 3 ans 3 %, à 4 ans 2,1 %. De 1952 à Juillet 1966 18 cas de glioblastomes de l'enfant vérifiés histologiquement ont été irradié, et 14 malades sont morts au cours de la première année, 2 au cours de la 2ème année, et un pendant la 3ème et la 4ème années. La médiocrité des résultats amène, après avoir discuté les problèmes de volume à irradier et de doses, à envisager des conditions d'irradiation en vue de la rendre moins contraignante pour le malade, ceci sous forme d'une irradiation tardive lors de la récidive.

SUMMARY

Seventy two adults with glioblastoma, in 69 of whom the tumour had been more or less completely extirpated, received roentgen treatment in the period between 1956 to July 1966. The rates of survival were: 6 months in 67 %, a year in 32 %, 2 years in 7.4 %, 3 years in 3 % and 4 years in 2.1 %. Eighteen children with histologically verified glioblastoma received roentgen treatment in the period between 1952 to July 1966. Fourteen of these patients died during the first year, two during the second, and one patient during each of the third and fourth years. In view of these poor results, and following a discussion of irradiation volumes and dosage, it is suggested that the patients may suffer less strain if irradiation after operation is given only in cases of recurrence.

ZUSAMMENFASSUNG

Zwischen 1956 und Juli 1966 wurden 72 Erwachsene mit Glioblastom, in 69 von denen der Tumor mehr oder weniger komplett exstirpiert war, mit Röntgenbestrahlung behandelt. Die Überlebensraten waren: 6 Monate in 67 %, 1 Jahr in 32 %, 2 Jahr in 7.4 %, 3 Jahre in 3 % und 4 Jahre in 2.1 %. In den Jahren 1952 bis Juli 1966 wurden 18 Kinder mit histologisch verifiziertem Glioblastom mit Röntgenbestrahlung behandelt. Vierzehn von diesen Patienten starben im ersten Jahr, zwei während des zweiten Jahres und je ein Patient im dritten und vierten Jahr. Mit Hinsicht auf diese unbefriedigenden Resultate und nach einer Diskussion geeigneter Bestrahlungsvolumen und Dosierung wird angenommen, dass man vielleicht den Patienten weniger Leiden verursachen möchte, wenn nur die postoperativen Rezidivfällen bestrahlt werden.

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NEUROSURGICAL CONSIDERATIONS AND CHEMOTHERAPEUTIC ASPECTS

M Da id

J ai ete particulierement sensible a l invitation de participer a cette Table Ronde et ceci pour deux raisons

Tout d abord parce que j estime que lors de la discussion des problemes con cernant la neuroradiologie la presence des neurochirurgiens s avere indispensable et aussi en raison du choix de la question faisant l objet de cette Table Ronde la therapeutique des glioblastomes cerebraux cauchemar des neurochirurgiens

En effet si du moins en France la necessite des specialites neuroradiologiques s est progressivement imposee et si desormais les problemes de diagnostic con cernant les tumeurs encephaliques ne sauraient etre resolus sans l intime et con stante collaboration des neuroradiologistes et des neurochirurgiens il n en est pas encore de meme vis-a vis de la therapeutique celle des glioblastomes en parti culier

Une experience de pres de quarante ans me permet d affirmer que la thera peutique des glioblastomes n a fait aucun progres decisif durant cette longue periode La chirurgie malgre ses resultats precaires demeure cependant seule valable jusqu ici la carence des agents physiques employes classiquement je dis classiquement etant demeuree pratiquement totale jusqu ici Ceci contraste avec les progres considerables realises dans le domaine du diagnostic pre-opera toire de localisation et de nature grace essentiellement à la confrontation de la clinique du gamma-encephalographie et de l angiographie Nous y avons longuement insiste avec Therese Planiol avec Dilenge et Sachs dans notre rap port à la Societe de Neurochirurgie de langue Française a Rennes cette annee

Nous ne saurions y revenir surtout apres les remarquables exposes de Mme Planiol et de Cronquist On peut dire d ailleurs que les quelques ameliorations obtenues en ce qui concerne les resultats chirurgicaux, tiennent essentiellement au fait que l on prevoit a l avance comment se presentera la tumeur que l on se propose d enlever aux progres de l anesthésie et de la reanimation beaucoup plus qu aux progres de la technique chirurgicale elle meme car depuis 40 ans nous

enlevons les glioblastomes de la même manière en cherchant à procéder à une ablation aussi complète que possible. Ces progrès tiennent également, comme vous le dira tout à l'heure Bernard-Weil, à l'institution du traitement hormonal pré- et post-opératoire. L'exérèse chirurgicale, même la plus large ne s'avère jamais complète en réalité et ne donne d'ordinaire que des survies de courte durée, dépassant très rarement 12 à 15 mois, la mort survenant d'ailleurs souvent dès le 6ème mois.

Quant à la mortalité opératoire, non négligeable, elle dépend de nombreux facteurs, en particulier de l'âge du malade, de son état, de la localisation et de l'extension de la tumeur.

Mais alors, me demandera-t-on, pourquoi opérer? Ceci pour plusieurs raisons : tout d'abord parce que c'est le moyen logique de lutter contre l'hypertension intracrânienne et l'oedème papillaire, ensuite parce que seule l'exploration permet de confirmer d'une manière absolue la nature glioblastique de la tumeur. Et l'on doit rappeler à ce propos que tous les neurochirurgiens possèdent dans leurs statistiques quelques très rares cas de glioblastomes dont la récidive ne s'est produite qu'au bout de longues années. Notons qu'il s'agit souvent dans ces cas de glioblastomes isomorphes. Par contre, je crois que les formes angionécrotiques sont d'ordinaire rapidement fatales. Sans mésestimer l'importance d'une résection chirurgicale la plus complète possible dans la genèse de ces bons résultats il n'en demeure pas moins que, dans ma statistique, 5 cas de glioblastomes authentiques enlevés incomplètement et non soumis à la radiothérapie, n'ont récidivé qu'au bout de 4 à 7 ans.

Comme nous le verrons plus loin, il est certain que le problème est plus complexe et que d'autres facteurs sont à considérer, en particulier ceux d'ordre métabolique et hormonal. Mais en dehors des cas où, du fait de leur siège polaire, l'exérèse large est effectivement possible, dans nombre de cas de glioblastomes profonds : glioblastomes du carrefour, glioblastomes étendus de l'hémisphère dominant ou glioblastomes à expansion bilatérale, on doit se borner à une ablation partielle correspondant à une décompression interne. Parfois, on doit même se résigner à la simple ablation du volet associée à l'hormonothérapie, selon la technique que nous avons préconisée avec Bernard-Weil. L'hémisphérectomie pratiquée par quelques-uns, outre sa gravité en pareil cas, n'empêche cependant pas la récidive.

Jusqu'ici l'association de la radiothérapie classique au geste chirurgical ne semble avoir amélioré que très légèrement et non toujours la durée de survie de nos malades. Certains, par contre, surtout avant l'institution du traitement hormonal, furent aggravés. Constans a discuté les résultats de cette radiothérapie suivant qu'elle est appliquée, après exérèse chirurgicale, après ablation du volet sans exérèse, ou encore crâne fermé. L'aggravation immédiate consécutive à

l application de rayons roentgen apparaît beaucoup moins frequente depuis l in stitution systematique du traitement hormonal

Devant les resultats encore decevants de la radiotherapie conventionnelle je me permets alors de vous poser la question suivante l evolution des techniques radiotherapiques permet elle d envisager une action plus efficace sur les glioblastomes? Depuis 1960 en effet nous avons connu la radiotherapie pendulaire la cyclotherapie les hautes energies depassant 500 ou 1 000 kV particulierement le cobalt Avez vous l impression que les resultats de la radiotherapie de 200 kV se trouvent depasses? Et moralement doit-on contraindre un malade, dont les jours sont comptes mais qui pendant quelques mois pourra mener une existence convenable, a une therapeutique trop souvent inefficace toujours fatiguante et chez lequel une hospitalisation prolongee et parfois aussi le mot de cobalt aggraveront l angoisse

Inversement certaines familles ne comprendront pas que l on condamne l opere sans tenter une radiotherapie Nous l acceptons toujours alors a condition surtout qu il s agisse d un sujet jeune

Mais je dois envisager avec vous un autre aspect du probleme therapeutique en vous posant la question suivante l implantation des isotopes radio-actifs dans un glioblastome represente t elle un progres therapeutique? Il y a 13 ans Talairach Ruggiero, Aboulker et moi meme dans notre service de Sainte Anne avions deja employe une telle therapeutique Les resultats furent alors assez *mediocres* Analysant les causes de ces demi echecs Talairach a revise le probleme et nous pouvons de son etude actuelle retenir quelques notions fondamentales Il *est bien* entendu que notre propos concerne exclusivement les glioblastomes *typiques et* non d autres categories de gliomes d evolution plus lente

Premier principe fondamental il faut que le glioblastome soit irradie en *to talite* c est dire l importance de la precision du diagnostic pre operatoire neuroradiologique et gamma isotopique particulierement en ce qui concerne l expansion tumorale Les verifications necropsiques demontrent en effet que les glioblastomes irradies incompletement recidivent *toujours par la peripherie*

Deuxieme principe, il faut que la tumeur soit irradiee d une maniere homogene sous controle stereotaxique a l aide de multiples particules per fo ales l irradiation est de l *ordre de 5 000 R* environ *Il* importe que l implantation des particules radio-actives depasse de 1 cm environ les limites theoriques de la tumeur c est dire qu *il n existe pas* de zone absolue de securite dans les glioblastomes volumineux affleurant les noyaux *gris ou le* tronc cerebral ou le corps calleux C est dire egalement que l implantation d elements radio-actifs apres exerese chirurgicale demeure contre indiquee *Le corps* radio-actif utilise par Talairach est l or 198 En raison de la courte periode de cet isotope (deux jours et demi) l isolement du malade est ainsi de courte duree L or 198 a donne a

Talairach de meilleurs resultats que l iridium radioactif seul ou associe a l or Quant aux *perles de cobalt leur emploi motive certaines reserves en raison des* radio necroses severes qu elles risquent de provoquer La mortalite operatoire dans les cas suivis par Talairach est reduite, la survie est en general de 15 a 20 mois *On* remarque une rapide disparition de l œdeme papillaire Dans les glioblastomes localises a des zones fonctionnellement importantes, les sequelles sont reduites au minimum, ce qui est un avantage important

Si, du point de vue de la survie, les resultats sont assez voisins de ceux obtenus par l ablation chirurgicale, il est par contre des cas ou la survie est considerable, ils concernent essentiellement les glioblastomes de petit volume diagnostiques precocement Depuis longtemps nous mettions l'accent, en le deplorant, sur le contraste entre le developpement croissant des moyens nous permettant de porter un diagnostic precoce de glioblastome et l absence de tout progres therapeutique dans le domaine chirurgical Des resultats comme ceux obtenus par Talairach doivent desormais nous rendre quelques espoirs en ce qui concerne la therapeutique precoce de certains glioblastomes J ose esperer que tout a l heure Constans et les radiotherapeutes nous apporteront a leur tour de nouvelles esperances

Il est encore plusieurs points que nous devons discuter ensemble

La *radiotherapie se montre t elle plus efficace dans les recidives*, les transformations malignes d astrocytomes, que dans les glioblastomes primitifs? Nous pensons ici, que l efficacite est parfois moins contestable si bien que nous recommandons *systematiquement l emploi des rayons lors de ces recidives confirmees* precocement par la gamma encephalographie Nous avons note en effet des remissions incontestables grâce a l emploi simultane de la radiotherapie et de l hormonotherapie en pareil cas

Et a ce propos, je desirerais vous demander votre opinion sur la radio sensibilite des oligodendrogliomes recidives En ce qui nous concerne, nous avons eu l occasion de verifier avec Constans l action indiscutable des rayons sur *les re cidives* de certains oligodendrogliomes operes plusieurs annees auparavant, *mais* ces resultats bien entendu, sont inconstants

Un autre probleme encore les hautes energies ne font elles pas courir d importants risques au cerveau sain avoisinant la tumeur? Il n en semble pas de même dans une irradiation intra tumorale precise avec une repartition homogene des doses Et avec Fischgold, nous pensons qu il est necessaire de pouvoir juger mieux qu on ne l a fait jusqu ici, des reactions cerebrales au cours du traitement

Certes, nous disposons de l echo median de l EEG, des radio-isotopes, de l arteriographie, mais est ce suffisant est ce meme valable, en raison de l œdeme? De plus, dans la plupart des cas il existe un manque de liaison entre le service de neurochirurgie ou sont pratiques les examens de contraste et dans les services specialises de cancerologie ou s effectue l irradiation Une exception les services

ou l introduction stéréotaxique de particules isotopiques est pratiquee par le neuro-chirurgien lui meme Certes cette dualite parait obligatoire nous le reconnaissons vu le rendement d appareils si couteux Mais cette dualite dis-je constitue a nos yeux un obstacle supplementaire Comment resoudre ce probleme pratique? Peut etre, notre ami Constans pourra t il repondre a cette question tout à l heure

En terminant, je desirerais exprimer mon etonnement devant le manque d interet presente jusqu ici dans notre pays tout au moins par les organismes officiels de lutte contre le cancer vis-a vis des tumeurs encephaliques Une liaison beaucoup plus intime avec les centres anti cancereux est necessaire d autant plus que les tumeurs cranio-encephaliques representent un pourcentage appreciable de cancers et qu ils different de ceux des autres organes par de nombreux points Il est indispensable que des credits plus substantiels soient prevus pour leur meilleure connaissance

Vous voyez donc que j ai pose beaucoup de questions a mes collegues rapporteurs J aimerais aussi que les auditeurs presents dans cette salle nous en posent a leur tour En effet une reunion comme celle ci ne saurait etre reellement benefique sans une franche et vivante discussion Je passe maintenant pour completer mon expose la parole a mon ami J P Constans qui va ciseler mon propos que j ai voulu tres general

J P Constans

Apres ce que vient de dire M David ce serait un lieu commun de repeter que les glioblastomes multiformes ont mauvaise reputation chez les neurochirurgiens

Leur augmentation quantitative dans les statistiques recentes des *differents* services est peut etre plus apparente que réelle pour les deux *dernieres decades* neurochirurgicales elle tient a une detection plus precoce grace au perfectionnement des procedes diagnostiques d une part et à un vieillissement *de la population* d autre part

Cliniquement c est la rapidite d evolution qui est la *principale* caracteristique des glioblastomes La duree moyenne totale c est a dire a *partir* du premier symptome e t de l ordre de 8 mois à un an

Vues sous un angle cancerologique ce sont des *tumeurs tres* particulieres du fait qu elles se developpent dans un espace clos, a l abri de la barriere hemo-encephalique Cette situation et l absence de voies *lymphatiques* a ce niveau expliquent leur evolution purement locale et par *consequent* les recidives in situ

Il faut neanmoins mentionner une centaine de cas *rapportes* dans la litterature de meta tases de gliomes en dehors du systeme nerveux celles-ci sont toujours

consecutives a un geste chirurgical et ont donc ete provoques par une dissemination sanguine per operatoire Le cas exceptionnel rapporte cette annee par Rubinstein du developpement spontane de metastases rachidiennes et ganglionnaires, en l absence de toute chirurgie, mais a la suite de l invasion par la tumeur du sinus longitudinal superieur, correspond au même processus

Mais des le depart et tout au long de leur evolution les glioblastomes se comportent comme une maladie de l organe dans sa totalite Sans doute s agit il la de phenomenes immunologiques La preuve en est donnee par les tentatives d hemispherectomies realisees par W Dandy, interventions qui se sont toujours soldees par des recidives plus ou moins tardives

A l appui de cette notion viennent les gliomes multiples ou les gliomes pluri focaux demontres dans plusieurs observations anatomiques Ceux ci seraient *moins frequents qu on ne l a imagine, car l etude histologique precise de certaines* de ces tumeurs a montre une continuite reelle entre les differents foyers

D ailleurs il faut retenir des essais de greffes tumorales effectuees dans un but immunologique, des travaux de Walker et de moi même, qu il s agit de cancers 'comme les autres Une fois transplantes au dela de la barriere hemo-encephali *que dans l organisme, les glioblastomes se comportent comme des cancers lympho* philes donnant lieu a une propagation par voie lymphatique et a des metastases d organes

Ainsi, ces tumeurs constituent une entite tout a fait exceptionnelle Leur evolution resulte essentiellement de deux processus (1) l envahissement progressif de zones fonctionnelles correspondant aux centres de la vie vegetative ou leur souffrance indirecte du fait du developpement volumetrique de la tumeur, (2) le developpement d une hypertension intracrânienne croissante, dûe soit au blocage des voies d ecoulement du LCR, soit a l installation d un œdeme cerebral par stase veineuse provoquee par la compression tumorale

C est generalement l HIC qui sera responsable de l aggravation terminale et du deces du malade par le processus de l engagement et des lesions qu il provoque dans le tronc cerebral

Pour echapper a ce mecanisme de l HIC ces tumeurs relevent par consequent en premier lieu de la chirurgie Nous nous trouvons en presence d une évolution aigue qui va rapidement menacer la vie meme du malade elle implique donc *en regle un geste chirurgical sans retard*

Cronqvist et Mme Planiol nous ont montre les progres realises dans le domaine du diagnostic Neanmoins, celui ci connait des limites et des insuffisances Il represente une presomption plus ou moins forte mais jamais une certitude Tous les neurochirurgiens ont en memoire des cas dans lesquels le diagnostic porte s est trouve infirme par l intervention A cet egard, un travail est significatif celui de Fix qui a effectue des contrôles autopsiques chez un groupe de malades di

agnostiques comme atteints de glioblastomes et qui avaient ete soumis sans vérification chirurgicale prealable, a la radiotherapie 3 cas sur 26 n etaient pas des glioblastomes (2 fois il s agissait de metastases et une fois d un meningiome intra ventriculaire)

C est pourquoi le geste chirurgical peut etre conçu comme une verification diagnostique Le pronostic des glioblastomes etant si pejoratif, il faut vraiment tout faire pour ne pas laisser echapper un cas d evolution moins navrante, et a fortiori un cas benin

Les nombreux travaux, celui de Davis en particulier, qui ont clairement fait apparaitre que les meilleurs resultats etaient obtenue a la faveur d exereses larges nous autorisent a ne pas remettre en cause cette question Mais le cerveau n est pas un organe homogene et cette exerese connait donc des limitations

Ce ont la les criteres d operabilite des glioblastomes qu ont tente de definir les neurochirurgiens de façon plus ou moins empirique et qui peuvent d ailleurs s appliquer a l ensemble des gliomes

Il en decoulera schematiquement plusieurs eventualites soit la chirurgie radicale, avec exerese macroscopiquement complete soit une chirurgie incomplete avec exerese sub-totale ou partielle soit une chirurgie decompressive avec simple biopsie ou meme sans biopsie soit enfin l abstention chirurgicale

Quels sont les criteres qui guideront le choix de ces differentes conduites chirurgicales? Ce sont essentiellement le siege de la tumeur et son extension au sein d un organe aussi heterogene que le cerveau Contrairement a la chirurgie classique du cancer cette propagation ne consiste pas en un envahissement du systeme lymphatique ou une infiltration des structures de voisinage mais bien a un accroissement sur place au sein meme de l organe

L exten ion de la tumeur aux formations profondes essentielles au maintien de la vie vegetative diencephale noyaux gris centraux tronc cerebral est consideree suivant les chirurgiens soit comme une contre indication absolue faisant abandonner toute chirurgie, soit comme une contre indication relative limitant le geste chirurgical a une exerese partielle a une biopsie ou a une intervention decompressive

Une autre consideration est d ordre qualitatif elle fait intervenir la notion de territoires anatomiques a haute valeur fonctionnelle lobe temporal gauche zone rolandique extension bilaterale Dans ces cas l attitude du chirurgien est dictee par des motifs individuels d ordre humain d ordre moral ou d ordre philosophique

Plus encore que dans n importe quel domaine de la cancerologie la qualite de la survie constitue la preoccupation majeure des chirurgiens vis a vis d une affection incurable Il faut que le déficit fonctionnel consecutif a la tumeur d une part et à l acte chirurgical d exere e d autre part se situe dans des limites ac

ceptables L attitude pragmatique doit s efforcer de sauvegarder au maximum l integrite fonctionnelle aussi longtemps que possible

On ne peut ignorer les cas de malades demeures pendant des semaines ou pendant des mois dans un etat purement vegetatif, pour lesquels une chirurgie moins ambitieuse aurait pu avoir des consequences immediates moins deplorables sans modifier l issue finale

D autres facteurs interviendront egalement, communs a toute la chirurgie, ce sont l âge, la condition generale du sujet, l attitude de la famille, le facteur geographique et enfin, la personnalite du chirurgien !

Mais il est bien certain que ces indications sont actuellement fonction de criteres macroscopiques Les donnees des examens diagnostiques sont forcement grossieres et imprecises prises sous un angle histologique

Les examens histologiques des cerveaux montrent malheureusement que les limites du glioblastome sont toujours au dela de ce que les moyens diagnostiques avaient defini, avec des infiltrations neoplasiques en peripherie au sein du parenchyme normal, avec des coulees tumorales, avec des propagations perivasculaires

Ces constatations ressortent d ailleurs des travaux de Concannon et Kramer (1960) portant sur 30 cerveaux de gliomes decedes en cours d'irradiation, et de Matsukado (1961) sur 100 cerveaux de gliomes grades 3 et 4

Apres Selverstone, nous avons pendant une periode de 3 annees de 1953—1955, effectue avec Ph Benda des contrôles systematiques per operatoires a l aide d un probe compteur de Geiger Muller pour determiner les limites tumorales et par consequent pour situer les limites ideales de l exerese Les malades avaient reçu une injection de traceur ^{32}P intraveineuse pre operatoire, isotope qui a le merite de se fixer de façon plus ou moins elective dans les tissus neoplasiques

Les resultats que nous avons obtenus chez ces malades ne nous ont malheureusement pas parus superieurs à ceux de la chirurgie habituelle

Depuis deux ans, en mettant a profit les travaux de Gouaze sur la fluorescence, nous avons egalement cherche a determiner opérativement les limites de l exerese

En ce qui concerne les tumeurs profondes le contrôle biopsique n est pas sans danger Le glioblastome est la plupart du temps une tumeur hypervasculaire Rappelons a ce propos que les hémorragies spontanees intra tumorales ne sont pas exceptionnelles Parfois même la simple decompression realisee par la taille d un volet avec ouverture de la dure mere suffit a provoquer une hemorragie intra tumorale comme nous avons pu le verifier a trois reprises chez des malades qui nous avaient ete adresses en vue d une radiotherapie et qui sont decédés en cours de traitement

La pratique des ponctions biopsies largement utilisee il y a plusieurs années, en particulier en Grande Bretagne, parait en voie de recul Il est apparu en effet

qu'elle était grevée d'une mortalité plus élevée que la chirurgie d'exérèse, mais il faut être juste en reconnaissant qu'elle s'adressait probablement à de plus mauvais cas.

Rappelons encore, comme l'a souligné Zülch, le caractère hétérogène de certains glioblastomes. Il arrive que des plages présentent les aspects d'une moindre malignité de grade 2 ou 3 au sein d'une tumeur. On ne peut méconnaître non plus le passage toujours possible d'un type de gliome à un autre correspondant à une malignisation comme ont pu le révéler des examens histologiques effectués lors de la récidive ou lors de l'autopsie.

Résultats de la chirurgie. La mortalité opératoire entre la plupart des mains telle qu'elle ressort des statistiques les plus importantes est de l'ordre de 15 à 20 %.

Je me suis efforcé, en analysant la littérature, puisque je ne disposais pas du temps nécessaire à une étude détaillée de mes propres cas, soit 245 glioblastomes opérés de 1952 à 1967 et 47 récidives, de classer un matériel des plus disparates et d'en tirer des conclusions communes aux différents auteurs.

On peut admettre en moyenne que 60 % des malades sont morts avant la fin du 6ème mois post-opératoire et que 10 à 15 % atteignent un an. La répartition des survies suit une courbe exponentielle. Si bien que dans toutes les séries y compris la nôtre, on trouve des cas ayant dépassé 3 ans et même 5 ans (de l'ordre de 2 à 3 %). — On doit cependant mentionner deux cas publiés par Elvidge en 1965 de survie à 23 ans et à 17 ans après l'intervention qui paraissent pouvoir être considérés comme les seules guérisons connues de la littérature.

Mais différents facteurs interviennent dans l'appréciation globale de ces résultats. Ceux-ci ont été bien mis en évidence par Hitchcock : (1) l'âge car la survie est meilleure chez les sujets jeunes, c'est-à-dire dans la tranche d'âge inférieure à 40 ans ; (2) le siège qui concerne surtout le découpage entre tumeurs superficielles et tumeurs profondes comme le constatent par exemple Roth et Elvidge ; (3) l'étendue : l'atteinte de 3 lobes écourte considérablement la survie alors que l'atteinte d'un seul ou de 2 lobes permet un pourcentage de 15 % de survie à un an ; (4) enfin la symptomatologie, la survie étant meilleure s'il n'y a pas d'HIC préalable. D'ailleurs pour tous les auteurs, confusion, torpeur ou coma sont des symptômes extrêmement péjoratifs à brève échéance. Il faut rappeler toutefois que les conditions diagnostiques ont changé au cours des dernières années, ce qui introduit un élément de disparité entre les différentes séries qui s'échelonnent sur des périodes de 10—15 ans et parfois davantage. L'introduction de la sériographie angiographique rapide, de la gamma-encéphalographie permettent des diagnostics plus précoces comme nous l'avons vu.

On peut donc espérer parvenir dans un proche avenir à détecter des glio-

blastomes encore 'petits'. Rappelons par exemple que Falconer, Gros et d'autres auteurs ont découvert des glioblastomes de petite taille lors de lobectomies temporales effectuées pour épilepsie temporale.

Par contre, les travaux portant sur du matériel d'autopsie ont, toutes proportions gardées, le défaut inhérent aux constatations faites pour d'autres cancers parvenus au stade de diffusion et entraînant l'exitus : ils ne rendent compte que d'un stade ultime de la maladie.

Dans l'appréciation des résultats intervient également une notion sur laquelle la plupart des auteurs ont mis l'accent et tout particulièrement Taveras et Hitchcock : c'est la qualité de la survie. S'il est toujours difficile de faire un pronostic de survie lors d'une intervention d'exérèse, les conséquences fonctionnelles sont parfois imprévisibles et les critères nous manquent. C'est la plupart du temps de sa propre expérience que le neurochirurgien déduira la conduite à adopter au cours de l'intervention.

Cependant il est parfois difficile de limiter une exérèse en cours d'intervention à une ablation partielle et on est conduit plus loin qu'on ne le désirait. Malheureusement la plupart des travaux ne font pas état de cette condition useful life ou useless life. D'ailleurs cet élément est difficile à mettre en évidence car il est dynamique. Souvent après une amélioration fonctionnelle post-opératoire, on assiste à une aggravation lorsque la récidive se manifeste cliniquement, entraînant des handicaps plus ou moins prolongés avant le décès.

Certains cas pour lesquels la récidive in situ donne l'espoir d'une deuxième exérèse satisfaisante font l'objet d'une réintervention. Nous en comptons 47 cas dans notre série. Il s'agissait dans plus de la moitié des cas de malades ayant subi une irradiation post-opératoire. C'est, en général, la réapparition d'un syndrome d'HIC qui nous a poussé à faire une nouvelle intervention, alors que l'état fonctionnel du malade était partiellement conservé.

La mortalité post-opératoire dans ces réinterventions est plus élevée : de l'ordre de 25 %. En dehors de 5 cas, la survie obtenue chez les autres, n'a jamais excédé en durée le délai écoulé entre la première intervention et la seconde.

C'est en fonction de ces résultats et avec la perspective de les améliorer par la mise en œuvre de traitements complémentaires que notre attitude chirurgicale actuelle est une attitude active. Sans vouloir anticiper sur ce que diront nos amis radiothérapeutes, la relative inefficacité de l'irradiation des glioblastomes confère encore la première place à la chirurgie.

La plupart des statistiques récentes, en dépit des difficultés d'interprétation qu'elles comportent pour une appréciation objective, se recoupent pour faire état d'un résultat meilleur de l'association chirurgie-radiothérapie que de la chirurgie seule et surtout que la radiothérapie seule (Bouchard).

Toutefois cette donnée se vérifie pour les tumeurs d'évolution rapide mais non

pour les survies dépassant un an qui atteignent sensiblement le même pourcentage dans les deux cas. Des considérations d'ordre radiobiologique encouragent cette attitude comme Jones y a insisté : si les cellules tumorales anoxiques et radio-résistantes qui constituent habituellement la portion centrale nécrotique, de la tumeur sont excisées sans compromettre la vascularisation des portions périphériques actives de la tumeur, l'efficacité de la radiothérapie se trouvera exaltée.

Il y a encore quelques années l'HIC à elle seule pouvait *justifier une chirurgie* même si le siège de la tumeur la rendait illusoire ou désespérée. Les mauvais résultats enregistrés lors des irradiations à crâne fermé qui comportaient un pourcentage élevé de décès survenus en cours même d'irradiation de l'ordre de 20 à 30 %, selon les auteurs, renforçaient encore cette indication. L'apport du traitement neuro-hormonal préconisé et largement diffusé par Bernard *Weil est d'une importance* considérable. Il est certain que la fréquente utilisation des solutions hypertoniques de tous types avait déjà représenté un progrès. Mais l'introduction de la corticothérapie puis la mise au point à la suite de recherches endocrinologiques d'un traitement à visée neuro-hormonale a eu pour effet de réduire considérablement le rôle néfaste de l'œdème cérébral. Il donne au chirurgien une beaucoup plus grande latitude dans ses *décisions, tout comme* aux radiothérapeutes en minimisant le rôle des phénomènes d'HIC toujours redoutables dans leurs *conséquences*.

A peu près systématiquement au cours des 3 dernières années nous avons *mis* en route un traitement de ce type dès que le diagnostic était établi et *parfois* avant même qu'il le soit. Celui-ci a été poursuivi jusqu'à la décision *de traitement* chirurgical ou non de même qu'au cours de l'irradiation.

Bien que cet aspect du problème relève davantage de Schlienger que de moi même puisqu'il *concerne* la *radiothérapie*, je me permettrai d'*en dire un mot* car il concerne aussi le chirurgien. Comme l'ont bien montré des études anatomiques *effectuées* par différents auteurs et en particulier par *Concannon*, Kramer et Berry, le centrage de l'irradiation s'avère *souvent insatisfaisant* et dans un pourcentage élevé de *cas insuffisant*. Il ne faut pas en effet minimiser les difficultés qui tiennent *essentiellement à deux* considérations se rapportant au centrage : (1) les examens diagnostiques sont des images pré-opératoires (angiographiques, gamma-encéphalographiques) avant exérèse plus *ou moins* complète de la néoformation et ne rendent pas compte de l'état post-opératoire. (2) les radiographies ne sont pas des reproductions en *grandeur réelle* et correspondent à un certain degré d'agrandissement dont il faudra *tenir compte*.

C'est pourquoi nous avons eu *recours* à l'emploi de repères métalliques. Ces repères radio-opaques sont placés *dans* la cavité d'exérèse en fin d'intervention qu'ils soient des clips d'*argent délimitant* les contours du lit tumoral ou *encore* de la poudre de tantale tapissant les parois. Ces repères *permettront ultérieure*

ment de suivre le retour du cerveau à des conditions normales lorsque les phénomènes de compression, d'œdème et d'hypertension et par conséquent de déplacement anatomique seront résolus.

Chimiothérapie. Parallèlement aux efforts des radiothérapeutes les chimiothérapeutes se sont aussi attaqués au problème du glioblastome. La vague croissante de la chimiothérapie anti-cancéreuse s'est naturellement étendue à ces tumeurs.

Depuis 1952, après French, plusieurs travaux isolés groupant de petites séries de cas mentionnaient *les tentatives faites dans ce domaine.* Malheureusement, de ce matériel hétérogène, il paraît difficile de tirer des conclusions, que les drogues utilisées soient des anti-mitotiques, souvent qualifiées de radio-mimétiques, en raison de leur parenté d'action avec les radiations, sur les mitoses, ou encore qu'elles soient des anti-métabolites agissant sur les métabolismes indispensables à la croissance cellulaire.

Dans les deux cas, il s'agit d'intervenir sur les phénomènes de multiplication cellulaire intense, sur le caractère de jeunesse propre à ces cellules et lié à leur croissance rapide, qui les rend plus vulnérables que les cellules normales. Le premier travail systématique effectué est celui de Simon qui a traité 54 cas de glioblastomes par un agent cytostatique alkylant, l'endoxan ou cytoxan. Des quatre groupes de malades traités ou par chimiothérapie seule intraveineuse, ou par chimiothérapie seule intra-artérielle, ou par chirurgie suivie de chimiothérapie, ou enfin par l'association chirurgie + radiothérapie + chimiothérapie, c'est le dernier qui comporte des survies apparemment supérieures au traitement classique. Les chimiothérapies seules ne semblent avoir donné aucun résultat et la chimiothérapie complémentaire de la chirurgie n'est pas probante. Il ressort néanmoins de cette étude que le produit franchit la barrière sanguine et exerce une action réelle quoique insuffisante sur les cellules néoplasiques.

Woodhall et Barnes, Jess, Llewellyn, Wilson ont de leur côté mis au point les techniques d'infusion et de perfusion carotidiennes. Il n'est pas dans mon intention de m'étendre ici sur des considérations de pure technique, mais alors que la perfusion artérielle pose peu de problèmes, l'infusion carotidienne nécessite la mise en œuvre d'une circulation extra-corporelle sur un malade anesthésié intubé et en hypothermie. Ces procédés bénéficient évidemment de l'expérience de la cancérologie générale.

Nous avons pour notre part une petite expérience des perfusions intra-carotidiennes portant sur 9 cas. Comme ces essais rentraient dans le cadre d'un projet du groupe d'étude des tumeurs cérébrales dépendant du groupement européen de chimiothérapie anti-cancéreuse (GECA), c'est la VLB que j'ai utilisée. En dehors de la constatation d'une tolérance relativement bonne de doses élevées de

cette vincaleukoblastine les resultats obtenus sur des recidives de glioblastomes n ont pas ete concluants le deces survenant dans les delais habituellement prevus

De meme toujours dans le meme programme de travail l emploi de la VLB et de l actinomycine D par voie generale parait etre negatif pour l ensemble de notre groupe apres une selection et une analyse assez rigoureuse des cas

Cependant un peu partout les auteurs ont eu recours a toute la gamme des anti cancereux depuis les alkylants avec les moutardes a l azote le thiotepa et l endoxan les antibiotiques avec l actinomycine D et la streptomycine A les anti metabolites avec le 5 fluorouracil et la methopterine A la vinblastine la vin cristine la leurocristine et plus recemment la mithramycine

Un travail de Kennedy en 1965 fait etat de 9 glioblastomes traites par la mithramycine Il a constate une amelioration dans 5 cas qui survecurent de 1 mois et demi a 5 mois Cependant le mode d action correspond a une inhibition de la synthese de l ARN et comporte donc une toxicite reelle pour l organisme

C est d ailleurs le principal danger de ces chimiotherapies et par consequent leur limitation Les agents les plus actifs sont en effet les plus toxiques pour l organisme en general ou pour le systeme nerveux en particulier

C'est pourquoi il n est pas possible d adopter une attitude optimiste vis a vis des possibilites actuelles de la chimiotherapie Compte tenu des resultats epars rarement interpretables avec rigueur on peut tout au plus lui reconnaitre un role adjuvant extremement restreint

Mais il ne faut pas sous-estimer les nombreux travaux conduits dans les la boratoires de recherche De nombreuses etudes sont effectuees chez l animal ou sur les cultures de tissu pour tester l efficacite des differentes drogues Il est probable que c est d abord dans ce domaine que seront realises les progres qui conduiront a une application clinique plus efficace

DISCUSSION

J Pecker

J'ai été très intéressé par l'exposé du Professeur Zülch. Cependant, il y a une question qui vient naturellement à l'esprit du clinicien. C'est la suivante: de temps à autre et je crois que l'on peut dire indépendamment des mécanismes réactionnels du cerveau (c'est à dire de l'œdème cérébral et des mécanismes d'engagement que vous avez rappelé) de temps à autre le comportement évolutif des glioblastomes est imprévisible, et nous connaissons les uns et les autres des glioblastomes que l'on nous a annoncés au Laboratoire comme particulièrement malins et qui ont comporté une survie de plusieurs années. L'inverse est vrai.

Je voulais donc poser la question suivante: est-ce que vous pensez, Professeur Zülch, que la morphologie nous permettra d'aller plus loin dans l'histopronostic des glioblastomes ou pensez-vous qu'il faille faire appel maintenant à d'autres techniques dont il n'a pas été question ce matin et je pense en particulier à l'histochimie?

K. J. Zülch

Ich möchte diese Frage in mehrere Teile aufteilen und zwar zunächst in die Frage der einheitlichen Klassifikation. Ich glaube, das ist das allerschwierigste Problem, denn ich habe in meinem Leben unter 8 000 Tumoren, die ich etwa klassifiziert habe, ein Glioblastom der hinteren Schädelgrube gesehen und Sie haben in den Statistiken heute eine grosse Zahl gesehen; das kann ein Zufall sein, das kann aber auch ein Unterschied in der Klassifikation sein. Ich habe Ihnen heute im ersten Teil ein polymorphes Oligodendrogliom gezeigt mit einer Verwilderung der Zellen, die jeden Normal-Pathologen dazu berechtigt, von einem der malignesten Gliome zu sprechen. Dieser Fall hatte eine Vorgeschichte von 3 Jahren und eine Überlebensdauer von 2 Jahren ohne Bestrahlung. Wenn Sie einen solchen Fall in einer Statistik mit Bestrahlung haben, dann ergibt er ein völlig falsches Bild und deshalb mein Hinweis auf den Versuch der internationalen Vereinigung der Cancerologen, heute eine allgemeine Klassifikation zu schaffen. Wir hoffen, dass in einigen Jahren, wenn die einzelnen Atlanten für

die Tumoren der verschiedenen Organsysteme da sind, bisher ist nur eine allgemeine Übersicht da, dass dann eine Unifikation in der histologischen Diagnostik moglich sein wird, das ist die erste Frage Die zweite Frage kann der Morphologe *aus dem histologischen Bild die Malignität voraussagen?* Das ist sehr schwer Das Medulloblastom ist ein äusserst zellreicher Tumor, es hat eine sehr starke Menge Mitosen und es ist hoch maligne Ein Oligodendrogliom kann die gleiche Zahl der Kerne haben, es *kann* eine *grosse* Zahl der Mitosen haben und trotzdem eine postoperative Überlebensdauer, sagen wir von 3 Jahren Wenn Sie nach den morphologischen Merkmalen allein gehen, mussten Sie eine falsche Diagnose stellen Die Prognose des Histologen hängt zur Zeit ab von den Erfahrungen des Neurochirurgen, erstmalig von der beruhmten Tafel von Bailey und Cushing und dann, was von den Kliniken in den letzten 30 Jahren gesammelt worden ist Naturlich wird man einen Fall mit so vielen Mitosen, wie ich Ihnen gezeigt habe bei dem einen Glioblastom, als hoch maligne ansprechen konnen, dazu berechtigt einen die Zahl der Mitosen, aber sonst haben wir in der Morphologie sehr wenig Moglichkeiten und bisher leider auch keine histochemischen Moglichkeiten, um eine echte Malignität des Wachstums voraussagen

S *Kramer*

I'd like to go a little more deeply into the same question We have discussed rather broadly the glioblastomas, calling them if you like, astrocytomas, grades 3 and 4 It seems to me that there is a very marked difference if it were possible *to separate the 3 from the 4, one thing we have not considered* at all, which I think may well be the cause of our failure, as I said before I do not believe entirely that we have failed because we cannot affect malignant cells in the brain but, I think we often fail because there is a great deal of hypoxia in the presence of necrosis The fact that there is so much necrosis particularly in the grade 4 gliomas makes me think that there is a great deal of lack of oxygen and therefore some marginal cells would be protected

Could Professor Zulch tell us whether in principle it is possible to divide grade 3 and grade 4 I know this is difficult and I know that there is a great pleomorphism in many tumors but there are exceptions

I have a personal communication from Dr Arthur Jones of St Bartholomew's, London, who tells me that his grade 3 gliomas (I don't know how he distinguishes them) now have an average survival of 40 months after radiotherapy *which is considerably better than most of ourselves* Whereas his grade 4 cases have an average survival of less than a year and a half, which is barely better

than the natural history Is there some way of dividing these two groups of gliomas? Does Professor Zulch think that the amount of necrosis present in the tumor prior to treatment will make a difference to the ultimate survival?

K J Zulch

Diese Frage mochte ich folgendermassen beantworten Das astropolymorphe wenn Sie so wollen semi maligne Astrozytom hat sehr oft oder meistens noch eine Impragnation der Zellen z B mit bestimmten Impragnationsmethoden wie dem Goldsublimat Man kann dadurch eine gewisse Differenzierung gegenuber dem primaren Glioblastom machen was sich niemals impragniert Das Zweite ist die Reihe der Eigenschaften die ich als das Ensemble des Glioblastoms be zeichnet habe die Ausbildung pathologischer Gefasse, die ich Ihnen gezeigt habe die Glomerulosbildung die kavernomartigen Systeme die fistulosen Ge fasse dann das Ausmass der Nekrosen und den Nekrosbiosen das heisst der langsam vor sich gehenden Degenerationsvorgange Ich glaube dass es in der Mehrzahl der Falle moglich ist ein polymorphes semi malignes Astrozytom des Grades 3 vom Grad 4 zu unterscheiden aber Sie mussen die eine Schwierigkeit kennen in der wir Morphologen immer stehen wir konnen unter Umstanden vom Neurochirurgen nur so ein kleines Stuckchen bekommen und dann sind einfach aus Mangel an Material unsere diagnostischen Moglichkeiten vollig ein geschrankt aber im allgemeinen wurde ich sagen insbesondere wenn man das Elektronenmikroskop heute in diese Untersuchung einschliesst ist eine solche Unterscheidung der beiden moglich Es gibt wie uberall in der Natur, fliessende Ubergange

M David

Je crois que toute cette discussion pour nous neurochirurgiens est d un interet capital mais je crois qu on oublie trop dans le pronostic des tumeurs a cote de l etude histologique l etude dynamique c est a dire le potential evolutif J ai toujours ete reconnaissant a Madame Planiol grace aux gammaencephalogrammes de nous fournir des donnees evolutives et de prevoir ainsi la transformation maligne d un astrocytome de type I ou II aussi il ne faut jamais perdre de vue que l etat metabolique et hormonal de l opere doit etre pris en considera tion Sinon comment comprendre les cas dans lesquels des glioblastomes indiscu tablement hypermalins sur les coupes histologiques et qui pourtant ont beneficie d une survie de plusieurs annees Il existe par consequent des facteurs d evolu

tivite dont ne rendent pas compte les images in vitro Comme en cancerologie generale, ce sont toutes ces transformations metaboliques et humorales qui doivent etre etudiees simultanement

Par ailleurs, je me permets de poser une nouvelle question aux radiotherapeutes un de vos buts est de limiter la necrose, tout en augmentant l action des rayons! n existe t il pas des conditions dans lesquelles serait place le sujet soumis aux rayons et qui augmenteraient la radio-sensibilite de sa tumeur tels que le caisson hyperbare ou l usage de certaines drogues

K J Zulch

Ich kann nur auf den ersten Teil der Frage antworten und Monsieur David nur dankbar sein Wir konnen als Morphologen ja nicht die dynamische Entwicklung verfolgen, denn der Neurochirurg operiert nicht alle 14 Tage und gibt uns ein Stuck des Gewebes zur Untersuchung Damit sind einfach die Grenzen des Morphologen festgelegt und die Moglichkeit die etwa Madame Planiol, eine solche Entwicklung dynamisch zu verfolgen, sind gegeben Fur den Morphologen bestehen sie nicht

S Kramer

I d like to answer the second part of Professor David s question, the question of hyperbaric oxygenation and radiation therapy It seems to me that in general we have reached a plateau in radiotherapy and we have reached the point Dr Legre has shown where we know, more or less, what the optimal dose is Besides let me say this, I am not so convinced that radio-necrosis of the brain is terribly common Of course it does occur but when you scan the world literature there is really a paucity of cases, something like 57 altogether and most of those have been treated in a way that many of us would not consider reasonable today very high dose, repeated course, and so on

As far as the hyperbaric oxygenation is concerned, the experience in the past has not been very satisfactory there are great difficulties as you know, of treating a patient in the chamber according to methods such as we use with conventional therapy because of the question of the fractionation The two groups that have done it, in the past namely Churchill Davidson in London and Van den Brenk in Australia have used rather large fractions and rather few fractions so that the total dose has been considerably lower than that which we now consider optimal The only experience which is still quite early is that of Chang,

at Presbyterian Columbia in New York who has been treating a randomized series of glioblastomas partly with hyperbaric oxygen and partly without and his early results seem to indicate that there may be some slight improvement

It is too early to say but I think personally that this is one area that we have to explore we have a lot of necrosis we have a lot of anoxia and it may well be that hyperbaric oxygen will give us a very substantial assistance

J Legre

En ce qui concerne la deuxieme question de Monsieur David le traitement par hyperbarie je dois dire que nous n en avons pas l experience, mais nous y avons pense et nous commençons maintenant a Marseille a traiter les cancers du poumon sous hyperbarie et je pense qu il serait interessant de traiter les tumeurs cerebrales avec cette technique la

M David

Le Professeur Zulch reprochait aux neuro-chirurgiens de leur donner trop souvent des trop petits bouts Dans les grands services de Neuro-chirurgie comme le notre a la Pitie comme dans certains autres nous operons malheureusement une dizaine de glioblastomes par semaine ce qui est d ailleurs navrant Et nous donnons a nos histopathologistes en particulier nous avons le Professeur Dalage ici present on leur donne souvent des masses extremement importantes de glioblastomes Or il est tres interessant de voir que certaines plaques ont l aspect parfois benignes et que d autres sont ultra malignes C est a dire qu une biopsie simple n a aucune valeur si elle n est pas positive Et ça c est un critere extremement important parce qu on dit ce n est pas un glioblastome et c en est un en realite mais on ne l a pas vu parce qu on ne l a pas coupe en totalite

K J Zulch

Ich glaube dass das was Professor David eben gesagt hat ist besonders wichtig fur die 20 % oder 30 % Falle ich weiss es nicht genau wie der Stand heute ist wo das Glioblastom keine angiographische Artdiagnose zeigt Naturlich kann die Randzone die eines grosszelligen Astrozytoms sein das ist aber jenseits der Kapazitat eines Neuromorphologen das zu beurteilen

M Lindgren

I would like to go back to the roentgenologic aspect and the isotope examinations and ask Dr Cronqvist and Mme Planiol if they have any experience in repeat examinations after operation, either with angiography or with gamma encephalography And, if repeat examinations have been made regularly, if it is possible to observe early recurrence

S Cronqvist

My own personal experience with gamma encephalography is fairly small We have, however, encountered great difficulties in evaluating brain scans after operation This is due to the fact that following operation there is an increased activity, confined to the soft tissue, in the area of operation It may persist for a long time and is often so marked as to conceal activity in tumour tissue beneath the area

M Lindgren

Generally the planning of the irradiation seems to be based on the pre operation roentgen films I just wonder Dr Cronqvist, if you also perform post-operative angiographies

S Cronqvist

We always carry out new angiographic examinations before and close to the application of radiotherapy

Mme Planiol

Nous avons fait beaucoup de gamma encephalogrammes apres l operation et l experience nous a montre que toujours apres l operation persiste une radioactivite qui est due au foyer operatoire Cette radio activite disparait d ordinaire dans l espace de 1 a 4 mois 1 mois pour les metastases, beaucoup plus long temps pour les glioblastomes dont les foyers ont disparu, au plus tot dans les deux mois Mais même lorsqu un foyer d origine operatoire n est pas disparu completement, il est possible de le reconnaitre par sa morphologie et en tout cas

il est possible, en le prenant comme référence pour la succession des gamma encéphalogrammes pratiqués après de voir survenir la reprise du processus néoplasique avant l'installation de nouveaux signes cliniques Cela, nous l'avons observé a plusieurs reprises dans des surveillances pratiquées systématiquement, et nous avons vu ainsi, 3 mois apres une intervention au cours de laquelle l'exérèse avait été macroscopiquement pratiquement complète, se reproduire le foyer d'une façon très nette sur le foyer opératoire les signes cliniques sont apparus 2 mois ou 3 mois après le foyer gamma encéphalographique Nous avons aussi suivi des malades traités par radiothérapie et nous avons de la même façon vu se développer la reprise du processus pendant ou après le traitement radiothérapique sans aucune modification apportée par celui ci nous avons observé la même évolution que chez les malades non traités Chez des malades traités par le radiocobalt dans les doses indiquées comme optimales par le Professeur Legré nous avons vu les foyers se développer et s'accroître de la même façon au cours de quelques mois (3 a 12) mais avec une différence considérable dans l'état clinique c'est a dire que les malades non radiotraités après intervention, et chez lesquels nous avons vu survenir une récidive ont présenté les signes cliniques de recrudescence tumorale beaucoup plus tôt Pour les malades traités au radiocobalt l'aggravation clinique se précipitait dans une évolution terminale, mais pendant des mois et des mois ces malades étaient restés relativement bien malgré le développement d'une volumineuse récidive dans des régions hautement fonctionnelles

M David

Je dois confirmer ce qu'a dit Mme Planiol que la gamma-encéphalographie est le meilleur procédé pour détecter non pas seulement dans les glioblastomes et *en particulier dans d'autres tumeurs du cerveau* les méningiomes précocement une récidive sans qu'il y ait encore reprise des signes cliniques Ça c'est une constatation que nous avons fait depuis des années et je dois confirmer absolument ce qu'elle vient de dire Maintenant ce n'est pas parce qu'un glioblastome dont les signes gamma-encéphalographiques ont disparu, que chez ce glioblastome on aperçoit grâce au gamma encéphalogramme une reprise des phénomènes que l'on doit réopérer Moi je suis contre la réopération des glioblastomes Ça ne sert à rien Je pense qu'à ce moment là il vaut *mieux faire* de la radiothérapie? Ça il n'y a pas de doute Mais réopérer un glioblastome qui récidive au bout de quelques mois pour moi c'est illusoire Je ne sais pas si c'est l'opinion de toute la salle et de ces Messieurs qui sont ici présents.

Mme Planiol

Je voudrais simplement rappeler le cas que nous avons vu à la Pitié, il y a quelques années, de ces rares malades qui ont des glioblastomes manifestement hétéromorphes d'emblée, incontestablement malins dans leur totalité sans qu'on retrouve de plaques différenciées même dans les coupes en série, et dont la survie est étonnamment longue. Monsieur Petit Dutaillis avait opéré le malade d'un énorme glioblastome occipital enchâssé comme une mandarine et parfaitement bien circonscrit, totalement malin. Les coupes ont été revues, dans la tumeur initiale et elles ont été revues dans les récidives. Je dis « dans les récidives » parce qu'en 12 ans, ce malade a présenté 3 tumeurs, qui étaient toutes les trois de même nature. Entre les deux premières interventions, il a repris son travail de maçon qu'il n'a dû cesser finalement que parce que son hémianopsie le gênait beaucoup trop. Mais c'est tout de même après 12 ans d'évolution que ce malade est mort. Nous en avons vu un autre récemment également dans une localisation occipitale qui a survécu 4 ans avec deux interventions et chez lequel également le diagnostic histologique ne laissait aucune place au doute quant à la dégénérescence. C'était d'emblée une tumeur extrêmement et totalement maligne. Du fait de l'existence de tels cas, l'effet d'un traitement n'est pas sans faire réfléchir.

M. David

Je répondrai à Mme Planiol qu'on cite toujours dans ce cas là, des cas de pièce, que la question qui m'avait été posée a été posée du point de vue général. Autrement dit, lorsqu'une tumeur dure plusieurs années, on a le droit de la réopérer, mais quand des signes gamma-encéphalographiques réapparaissent au bout de quelques mois, et qu'on sait pertinemment que c'est un glioblastome polymorphe, la règle c'est de ne pas réopérer, parce que les résultats sont illusoires ou du moins extrêmement peu importants et on augmente très souvent les troubles fonctionnels. Alors moi j'aime mieux la radio-thérapie. Je crois que Monsieur Constans veut dire un mot.

J. P. Constans

J'ai parlé tout à l'heure des réinterventions aux récidives qui représentaient dans ma statistique 47 cas pour 245 glioblastomes opérés. J'ai signalé que la survie obtenue à partir de ces réinterventions était généralement plus courte que

la survie obtenue apres la premiere intervention sauf pour 5 cas et peut etre ces 5 cas valent ils la peine d etre mentionnes car au moins pour 3 cas il s agissait de recidives qui a l intervention et a l examen histologique ne sont pas apparus tumorales mais sont apparus radiosclerotiques ou radio-necrotique L examen histologique systematique n a pas montre de traces de cellules tumorales et ce sont des malades qui ont eu des survies de 3 a 7 ans et plus puisqu il y en a une qui est actuellement encore en vie alors que la recidive etait survenue dans les mois qui ont suivi la premiere intervention

S Cronqvist

Professor David I would like to hear your opinion about the possibility to make an operation based solely upon the information obtained from gamma encephalography

M David

Je crois que dans l etat actuel des choses et quand l etat du malade le permet on ne doit pas se contenter d un simple scanning pour operer et je pense qu il est de l interet du malade et du neurochirurgien de s entourer tout de meme d un certain nombre de donnees anatomiques morphologiques pour savoir comment est faite cette tumeur et je ne pense pas etant donne qu on n est pas du tout sur de la nature avec le scanning dans un certain nombre de cas Mme Planiol nous l a rappele tout à l heure puisqu elle a montre que dans 60 % elle avait la nature il faut faire d autres examens non seulement par regroupement de l arteriographie et du gamma encephalographie augmenter beaucoup les chances de detecter la nature mais aussi parce que le neurochirurgien doit savoir comment est faite la tumeur qu il opere de savoir ses pedicules de savoir son extension Et bien il n aura pas tout cela avec le scanning et a moins qu il y ait une urgence absolue je ne pense pas qu on doive operer un glioblastome sans arteriographie au moins tout au moins

Mme Planiol

Je suis entierement d accord et je le suis d autant plus que si dans la plupart des cas les 2 examens la gamma-encephalographie et l angiographie quelque soit leur chronologie laissent prevoir le meme volume tumoral Il n en est pas

1 [illegible] R [illegible] Th [illegible] Phy [illegible] Biol [illegible] (19[illegible]9)

toujours ainsi et cela est heureux. Les deux examens, ensemble, permettent en effet quelquefois de se faire une idée beaucoup plus précise de l'extension de la tumeur, en particulier quand elle est kystique, quand elle est hétérogène bien vascularisée à un endroit que montre bien l'angiographie, et moins bien vascularisée, ou par des vaisseaux trop petits dans une autre zone, que montre bien le gamma-encéphalogramme. Nous avons pu récemment assister à une intervention chez un patient dont le gamma-encéphalogramme montrait un foyer typique de glioblastome au niveau de la corticalité et de la région immédiatement adjacente, et n'indiquant pratiquement aucune extension en profondeur. L'artériographie dans ce cas montrait une lésion expansive probablement importante mais à peu près totalement avasculaire. C'était bien un glioblastome avec deux énormes kystes dans la profondeur que ne voyait pas le gamma-encéphalogramme, qui avait mis en évidence la masse pleine cellulaire de la superficie.

S. Cronqvist

I have two questions to ask. The first is to Dr Constans. As was evident from my communication, neuroradiologic procedures are not too reliable in determining the degree of malignancy. Because of this it is important to verify the diagnosis of a malignant glioma before radiotherapy. Is it your routine, Dr Constans, always to make a biopsy before therapy? My second question is to Dr Kramer. The figures mentioned by you indicated that the information obtained with neuroradiologic procedures is in fact fairly inaccurate. My question is: were really all the possibilities of neuroradiology utilized, that is, was encephalography performed in addition to angiography and, in case angiography alone was performed, was it serial angiography?

J. P. Constans

Je pense avoir dit que l'attitude actuelle que nous avions adoptée en relation avec les radio-thérapeutes de l'Institut Gustave Roussy était une attitude activiste dans la mesure où la plupart des glioblastomes diagnostiqués faisaient l'objet d'une *intervention préalable*. Quand je dis intervention, c'est en général une intervention d'exérèse, celle-ci étant une exérèse aussi large que possible quand cela est réalisable, ou une intervention limitée. La pratique des ponctions est pratiquement extrêmement réduite aux tumeurs profondes et encore avec beau

coup de precautions dans la mesure ou elle represente un certain risque chirurgical et ne donne pas toujours une indication suffisante du point de vue histologique

S Kramer

To answer Dr Cronqvist about the number of studies, of course we didn t have time to go into that in detail 17 patients had ventriculography only 6 had both pneumography and carotid angiography, 3 had angiography alone and 2 patients had an air cystogram and carotid angiography I think the problem is not that the radiologist fails to recognize a space occupying lesion this he does very well and so does Mme Planiol but I don t think it can be recognized to the extent where every last centimeter of it is demonstrated so that you can arrange your field in such a way as to include it This is the point the degree of accuracy not the fact that you cannot or can show it

J Legre

Vous avez vu les resultats statistiques que je vous ai rapportes concernant les irradiations post-operatoires des tumeurs cerebrales par gamma therapie ou par radio-therapie de nombreux radio-therapeutes sont ici presents et je voudrais demander a Mr Martin Lindgren a Mr Dutreix et à Mr Schlienger s ils ont constate les memes faits que moi et s ils l ont constate s ils pensent que nous avons le droit d irradier un glioblastome par hautes energies si les resultats par radio-therapie conventionnelle sont superieurs ou tout au moins moins mauvais

J Dutreix

La question que vient poser Monsieur Legre me parait etre une question extremement difficile a aborder parce que a priori la raison pour laquelle les resultats seraient differents pour les hautes energies et pour les basses energies m echappe completement On peut tres bien admettre qu il n y ait pas d avantages à utiliser le cobalt plutot que les rayons roentgen 250 kV mais je ne vois vraiment pas pourquoi avec une disposition de doses qui ne peut pas etre plus mauvaise que par la radiotherapie conventionelle le telecobalt donnerait de moins bons resultats que la radiotherapie classique

Je pense, pour la même raison d ailleurs que nous n avons pas a esperer que d utiliser des rayons roentgen de 24 MeV, ou des electrons nous conduirait a des resultats sensiblement plus eleves

Alors je n ai sans doute pas repondu a votre question mais en fait je ne vois pas comment je le pourrais

M Lindgren

My own experience is that the results are about the same with conventional radiotherapy as with cobalt 60 But, I have the feeling that with high voltage therapy you give a more uniform dose to the part of the brain to be irradiated, and this means a higher risk of irradiation injury to the small vessels It therefore seems appropriate to use a lower dosage with high voltage therapy than with conventional radiotherapy

S Kramer

It seems to me that the extra volume irradiated, even if the same port is chosen because of side scatter is considerably larger when using conventional voltage (200 or 250 kV) than when irradiating with cobalt Therefore, your results are better

J Pecker

Je voudrais poser une autre question aux moderateurs et a l ensemble des discutants C est une question difficile, celle de l intérêt pratique du diagnostic precoce des glioblastomes

Nous pensions, jusqu a maintenant qu un signe, au moins, avait une certaine valeur dans ce diagnostic precoce l injection des veines de drainage Or nous savons, depuis ce colloque que les accidents vasculaires comportent egalement, et Mr Cronqvist l a rappele, des injections vasculaires precoces qui rendent donc le diagnostic particulierement delicat J en arrive donc a ma question

Est ce que ce diagnostic precoce est reellement important ou est ce qu il ne represente qu une satisfaction d ordre intellectuel Car, personnellement neuro chirurgien je n opererais jamais un glioblastome sur ces signes mineurs imprecis et discutables que l on essaie de nous decrire actuellement

Je ne sais pas quel est l avis des autres neurochirurgiens je sais moins encore quel est l avis des radiotherapeutes Est ce qu ils entreprendrons une irradiation precoce sur cette micro-semiologie angiographique?

Enfin je voudrais demander si un seul d entre vous neuro-chirurgiens ou radiotherapeutes osera affirmer que les resultats therapeutiques eloignes seront moins decevants si le traitement a ete applique a ce stade tres precoce?

S Cronqvist

I would like to answer the first part of the question In Sweden it is at present o that an increasing number of elderly people is received at the hospital and an increasing number of angiographic examinations are performed in these patients As a result the finding of early filling veins is a common one I am repeatedly put in the position to make a differential diagnosis between tumour and a cerebro-vascular lesion which as mentioned before, may present on the angiogram with similar changes Thus the early filling veins noted in cerebro-vascular lesions are definitely not only of theoretical interest but has in fact a great practical importance

J Legre

En ce qui concerne la deuxieme question qu a posee le Professeur Pecker je pense que nous n avons pas le droit d irradier un malade pour lequel nous n avons pas de preuve histologique si ce n est pour ameliorer nos statistiques

M David

Justement Pecker vient de donner de l eau a mon moulin quand je disais tout a l heure que pendant tres longtemps j avais ete absolument desole d assister au developpement de plus en plus grand des procedes diagnostiques devant l inanite ou la mediocrite de nos procedes therapeutiques c est pour ça que justement j ai pose le probleme le probleme de ces radio-isotopes in situ mais je ne pense pas qu il faut le faire quand il y a une veine qui apparait je ne pense pas non plus qu il faut le faire quand il n y a pas de symptomes Alors tout le probleme est tres grave parce que est ce que lorsque on operera, la tumeur ne sera pas de

venue en pratique inopérable. C'est le problème des lésions primitives. Si nous avions à notre disposition un procédé certain, nous aurions le droit de la faire, étant donné que dans le fond nous aggraverons peut-être la maladie en donnant des troubles fonctionnels et que nous ne savons jamais comment évolue un gliome, je crois qu'il faut être extrêmement prudent. Mais là le problème, est un problème humain, un problème philosophique en quelque sorte. C'est une décision qui est à prendre, en étudiant tout le contexte familial et c'est très difficile.

J. Fischgold

Pour la question du diagnostic précoce qu'on vient de nous poser, je crois, qu'en matière de glioblastome, le problème n'est pas aussi grave que pour les autres tumeurs cérébrales et j'en ai deux éléments à vous fournir.

1. M. Tempis qui a beaucoup étudié l'histoire naturelle des tumeurs cérébrales, et il les a étudiées à l'Institut Max Planck avec Zulch pendant de très longues années, nous dit d'une manière assez claire dans ses derniers textes que toute tumeur qui n'a pas fait ses preuves dans les trois premiers mois, *n'est pas un glioblastome*. C'est une forme un peu détournée pour nous dire que le glioblastome fait très rapidement ses preuves par la totalité de ses signes et par la gravité de ses signes.

2. Avec Mme Planiol nous sommes allés, il y a trois ans, à Cologne, dans un colloque qui discutait le diagnostic précoce des tumeurs cérébrales et ceci nous a obligé Mme Planiol et nos collaborateurs de revoir nos statistiques du point de vue de la précocité et notre surprise a été assez grande de voir que, surtout en matière de glioblastomes, toutes les méthodes que nous faisons intervenir, et nous sommes une maison dans laquelle nous faisons intervenir de manière régulière la neuroradiologie, le gamma, l'électro-encéphalographie et depuis quelques années, c'était déjà le cas à Cologne, l'écho.

Toutes ces méthodes n'ont pas amélioré le diagnostic précoce. Je crois que pour le glioblastome dans 2 ou 3 mois on sait toujours qu'on a à faire à un glioblastome, je dirais presque sans examen complémentaire, David. Les examens complémentaires ne nous disent pas que c'est un glioblastome. Ils nous disent *où, comment, quel volume, quel rapport, et tout cela est très important. Ceci me paraît* tellement vrai que je finis en vous rapportant un mot de M. Mascherpa qui était le Directeur de la Neuroradiologie à l'Institut Neurologique de Milan, et qui, un jour me disait, c'est pas avant hier, « je suis content, j'ai franchi 65 ans, j'ai tout au moins échappé au glioblastome ».

Le glioblastome a une histoire naturelle qui fait qu'au contraire de l'astrocytome et du méningiome, il n'a pas tant de trahisons à nous fournir, je crois.

M Schlienger

Je ne suis pas certain que le diagnostic precoce des glioblastomes soit reellement le probleme essentiel qui realise un progres substantiel dans les survies obtenues Il arrive que fortuitement certains chirurgiens aient pu operer des glioblastomes de taille tres microscopique Ceci s est verifie nous le savons tous dans les lobectomies temporales effectuees par exemple pour epilepsies temporales Les survies n ont pas ete ameliorees pour autant Je crois que reellement le probleme est beaucoup plus immunologique

Je le disais tout a l heure d un point de vue cancerologique il semble que le glioblastome soit un cancer de tout l organe et d un organe qui se defend mal Evidemment notre souhait a tous c est d elargir ce faible pourcentage de cas qui depassent des survies de 3 ans ou de 5 ans ou davantage puisque dans la litterature on retrouve sous la plume de Monsieur Eluige deux cas de guerisson ou pouvant etre consideres comme tels de glioblastome C est d ailleurs les deux seuls cas qui ont depasse 17 ans et 23 ans respectivement, apres intervention et apres des verifications histologiques multiples Donc notre souhait a tous c est evidemment d elargir ce pourcentage

Je pense que c est beaucoup plus a la faveur de recherches dans le sens immunologique qu on pourra assurer une meilleure defense de l organisme et spécialement du cerveau vis-a vis d un cancer qui doit sa malignite du fait qu il a comme caractere specifique de se passer a l abri de la carriere hemo-encephalique mais aussi sans defense lymphatique

K J Zulch

In diesem Augenblick unserer Diskussion mochte ich zu dem was Herr Contans gesagt hat aus der allgemeinen Cancerologie hinzufugen Es gibt jetzt eine besonders interessante Art von experimentellen Tumoren die diaplazental wirken ahnlich wie seinerseits das Thalidomid Entwicklungsmissbildungen hervorrief Dabei wird einer Ratte z B am 13 —19 Tag der Schwangerschaft ein Cancerogen aus der Nitroamminreihe einmal gespritzt in einer Dosis die etwa 1 5 einer Normdosis *ist um einen Krebs zu erzeugen* d h einer unterschwelligen Dosis Praktisch bekommen alle Kinder der Schwangerschaft alle Jungen dieser Ratte einen Tumor wenn eine bestimmte chemische Komposition gegeben ist einen Tumor des Nervensystems dabei etwa 30 %—40 % Zentralnervensystem 10 % 15 % Ruckenmark und die ubrigen in der Peripherie besonders am Trigeminus am Plexus brachialis und an den ubrigen peripheren Nerven

einschliesslich des Vagus. Das ist nun ein ungeheuer interessantes Modell, zumal sich mehrere Dinge finden, die von ungeheurem Interesse sind. Das eine ist, dass es eine Prädilektion auch in der Topik gibt, genau wie wir sie von den Hirntumoren kennen, etwa für die Gegend des Ammonshorns. Die zweite, dass bei allen Untersuchungen, die bisher gemacht wurden bei der jungen Ratte bei der Geburt, morphologisch, wir wissen noch nicht, ob elektronenmikroskopisch, aber mit den konventionellen Methoden nichts zu entdecken ist, von einem malignen Wachstum, das heisst, der Kern in einer bestimmten Zeit der Entwicklung getroffen vom Karzinogen, erhält eine Umwandlung, die dazu führt, dass er 150 Tage später an einem Karzinom erkrankt und zwar an einem Karzinom, was offensichtlich eine Krankheit ist, die man gar nicht beseitigen kann. Dieses Modell wird später sicher die Möglichkeit geben für die Allgemeincancerologen in der interessantesten Weise hin und her zu spielen und vielleicht manche Probleme lösen, die wir heute nicht kennen und ich erwähnte, dass sehr oft bei der systematischen Untersuchung eines Glioblastoms jenseits einer relativ scharfen Grenze nichts zu sehen ist. Der Tumor scheint vom Neurochirurgen total entfernt zu sein und trotzdem haben wir das Rezidiv in einem halben Jahr.

M. Lindgren

I think we have reached the point where we have heard that neurosurgical cure of malignant glioblastoma is of varying permanence, and we have heard that radiotherapy gives results which may be somewhat improved by combining with other post operative therapy. And I think it is not so important further to discuss the various methods of radiotherapy because the newer methods, such as electron therapy and therapy with protons, are still very new and results from long time observations have not been given. There are results in the literature with survivals of more than 10 % of patients with malignant glioblastoma after combined surgery and radiotherapy, using conventional roentgen therapy. If we consider this figure, and what we can do in cases of carcinoma of the stomach or oesophagus, then we find that the results are not so unsatisfactory. We therapists and others who often see patients with malignant disease anywhere in the body, do not therefore feel as disappointed as maybe you feel, Dr David, because we believe we can do something for the patients, and our intention is to better what we can do, and you ask how to achieve this. We could treat the whole brain and Dr Kramer has said that in cases of glioblastoma the whole brain should be irradiated. We have also heard of chemotherapy which treats the whole brain,

and I think this maybe could provide a better approach — Then of course new problems are posed problems of dosage — But the possibility to irradiate both the hemispheres in more advanced cases offers perhaps a means of tackling the problem The problem of anoxia is another one and maybe cooling of the patient may also be of some value This has not been discussed from the surgical aspects but radiotherapists have considered it But all this is just things in movement and comments on such possibilities would be interesting

R Lorenz

Wir haben von Herrn Zulch gehort daß es in der Radiotherapie 2 Faktoren gibt die maßgeblich sind Der eine ist die Wirkung in der Umgebung des Tumors vor allem an den Kapillaren bzw an den kleinen Gefaßen Der zweite ist die Wirkung in der Zelle selbst Ich glaube daß wir uber letzteres nicht sehr viel wissen Wenn wir uns aber jetzt als Radiotherapeuten uberlegen, daß wir seit fast 40 Jahren Radiotherapie des Hirns betreiben, so kann man nicht behaupten daß wir am Anfang und noch im Versuchsstadium stehen sondern wir wissen aus der enormen Zahl von Fallen die uberall bestrahlt worden sind daß beim Glioblastom eine bestimmte Dosis die nicht unter 4 000 R und etwa um 6 000 R liegt die beste Wirkung zu haben scheint Dort wo bis zu 26 000 R gegeben worden sind ist das Endresultat nicht entscheidend besser geworden Ich mochte hier die Frage stellen ob wir nach diesen Jahrzehnten der Beobachtung und des Sammelns unserer Ergebnisse nicht doch ein gewisses Optimum der Bestrahlung von dem ich personlich glaube daß es bei 6 000 R liegt gefunden haben Es ist wohl doch auch so daß bei den Fallen die wir zwei und dreimal wegen Rezidivs bestrahlt haben und denen wir das Mehrfache der oben genannten Dosis gegeben haben die Gefahr besteht daß wir nicht mehr den Tumor selbst beeinflussen sondern in viel großerem Maße das gesunde Hirngewebe Welche Rolle hierbei die Bestrahlung spielt betonte bereits Herr Zulch wissen wir nicht genau Es ist interessant daß man bei Durchsicht der alteren Literatur aus den Jahren 1920 bis 1925 Falle findet bei denen Patienten kleine Dosen etwa aus Grunden der Epilation temporal oder occipital verabfolgt worden waren die spater im Hirn zu Herdzysten bzw Zerstorungsherden gefuhrt haben Dieses sind so kleine Dosen die nach unserer allgemeinen Ansicht noch nicht gewirkt haben konnen Nun wollen wir doch als Therapeuten nach dem Motto handeln nil nocere Ich finde es daher nicht gut wenn man weiß daß unter gewissen Umstanden, die uns noch nicht ganz bekannt sind Kleindosen schaden konnen daß wir dann an Hochstdosen herangehen die gewiß schaden werden Fur mich heißt das den Teufel mit dem Beelzebub auszutreiben Deswegen frage ich ob auch Sie als

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M Lindgren

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S Kramer

There is no doubt that when one goes into these fantastic figures one has to expect damage Two aspects about it First of all in reviewing the statistics from the past you mentioned the fact that damage was encountered after very high doses. But if you look a little bit more closely at these past reports you will find that there are patients who were treated for epilation and also had necrosis of the skull Well necrosis of the skull is not caused by 400 rad So clearly the doses given must have been much larger than those measured or calculated

The econd problem is a more modern one we have as radiotherapists to tackle the problem of fractionation We are talking about 6 000 rad in 6 or 7 weeks This implies that we are talking of heavy doses But it has been shown quite clearly that it is not only the overall doses or the time that matters it is also the number of individual fractions

If we are going to treat a patient three times a week and give him the same do e (which is in the maximum tolerated range) as if we were to treat him every day the chance of producing necrosis is excellent and if we are going to treat him at weekly intervals then we have to reduce the dose very markedly Radio biologically the individual fractions are very important and this has in my opinion not been sufficiently recognized

E Bernard Weil

J ai ete tres interesse par ces remarques qui ont ete faites a l Hopital Saint Antoine et que j ignorais A notre avis, la gamma encephalogramme est un element tres important pour suivre une therapeutique quelqu elle soit et le traite ment de l œdeme cerebral en particulier et si je ne vous ai montre aujourd hui que des arteriographies ou des electroencephalographies il est vrai que nous aurions pu aussi faire allusion a quelques enregi trements gamma encephalographiques Et ceci est tres important car le Professeur David m a toujours demandé i avec ce traitement hormonal qui modifiait l equilibre biologique nous avions une action qui se limitait purement et simplement a l œdeme cere bral ce qui n est deja pas mal pour un glioblastome — ou s il y avait egale ment une influence sur l evolution du processus cancereux lui meme Nous avons ete toujours prudents en la circonstance Simplement nous accumulons des faits nous recherchons d autres elements en faveur d une influence de l hormone antidiuretique dans l evolutivite du cancer cette etude deborde le cadre des glioblastomes puisque nous avons etudie le comportement de culture de tissus tumoraux-cerebraux in vitro au contact de la vasopressine puisque nous avons

Radiotherapeuten der Meinung sind, daß man sich im Hinblick auf die uns vorliegenden Erfolgsstatistiken nicht doch bei der bisher bewährten Dosis von etwa 6 000 R halten soll, wenn man nicht Gefahr laufen will, starkere Schaden zu setzen Das ist meine Frage, die ich hier stellen mochte

J Legre

Je crois que nous avons, tout a l heure, expose le probleme de la dose optimale Evidemment, comme le dit l interlocuteur, nous ne pouvons nous baser que sur l experience passee et ceci nous a amenes a conclure d apres les statistiques que nous avons faites, qu il semblait qu il y ait une dose optimale entre 5 000 et 7 000 rad et je suis tout a fait de son avis, en definissant, s il le veut, cette dose de 6 000 qui est une zone intermediaire entre 5 et 7 Je crois qu il est quand meme difficile de preciser exactement au rad pres la dose optimale

En ce qui concerne les effets nocifs des doses fortes, je lui en ai parle, je vous en ai parle tout a l heure dans mon expose Je n ai jamais donne de doses aussi fortes que celles qu il nous a citees puisqu il nous a parle de 20 000 rad, ce qui est une dose evidemment enorme Mais mes doses maximales se situaient a 10 000 ou 12 000 rad, et deja a 10 000 ou 12 000 rad on constatait l effet certainement nefaste de la radiotherapie

Donc, d apres l experience des annees passees et d apres les statistiques faites, je crois qu il est quand meme une notion qui est acquise c est celle des hautes doses nocives Quant a la dose optimale eh bien, on peut la fixer comme nous l avons dit tout a l heure entre 5 et 7 et si vous le voulez a 6 c est un chiffre moyen entre 5 et 7

M Jacquinot

A propos des phenomenes biologiques generaux qui pourraient intervenir dans l evolutitivite des glioblastomes j aimerais demander a Mme Planiol et a Monsieur Cronqvist, s ils ont pu observer, comme nous l avons nous memes fait dans le laboratoire du Professeur Boudin a l Hopital St Antoine, le fait suivant lorsque l on soumet un sujet qui est porteur d un glioblastome au traitement propose par le Professeur David et Monsieur Bernard Weil on constate litteralement sur le plan gammagraphique une fonte non seulement topographique mais du foyer d intensite isotopique Nous avons ete amenes a faire cette remarque a propos de plusieurs malades et j aimerais connaitre leur opinion a ce propos

DAVID expressed the opinion that treatment of the tumour is the nightmare of neurosurgeons Neurosurgery has developed better methods of operation an aesthetic techniques have been refined, and pre and postoperative hormone therapy is now available Surgical extirpation is however, never really radical and the average duration of survival is 12 to 15 months, most of the patients dying within six months The operative mortality is 15 to 20 per cent Surgery is nevertheless necessary to reduce high intracranial pressure and to obtain a definite histologic diagnosis The site of the growth is often such that only a relatively small part of the tumour can be excised CONSTANS discussed palliative therapy with chemotherapeutics administered by different techniques and reported that the results obtained so far are encouraging Glioblastoma multiforme seems to be an immunologic problem a cancer involving the entire brain

The actual situation of radiotherapy was discussed by KRAMER, who concluded that the whole brain should be irradiated and by LEGRE who suggested that the whole hemisphere in which the tumour was situated should be similarly treated SCHLIENGER felt that irradiation should be given only to patients with postoperative recurrence Conventional radiotherapy (180—250 kV) and ^{60}Co therapy as well as various fractionation schemes seem equally unable to improve the poor prognosis

From the point of view of the radiotherapeutist we now know the optimal dose capable of affecting this neoplasm without injuring the healthy surrounding tissue We have reached a plateau from which attempts can be made to approach the treatment of glioblastoma multiforme from different angles Hyperbasic oxygenation in connection with radiotherapy has hitherto not proved very rewarding mainly because of difficulties encountered in fractionation of the total tumour dose The individual fractions of radiation are important from a radiobiologic point of view both the number of fractions and the individual tumour dose in relation to the overall time dose relationship The value of the quality of the radiation in glioblastoma multiforme is not yet properly understood Only randomized studies with regard to survival particularly useful survival can provide the answer Such investigations for example with high energy electron and proton irradiation are in progress and the preliminary results appear encouraging External irradiation enables a better dose distribution than the intracranial application of radioactive sources and diminishes the risks of undue late reactions

We must try to find a method for demonstrating the total extent of the space occupying lesion so that treatment can be properly planned

Steroid therapy in connection with other methods of treatment has made it possible to treat a larger percentage of patients because of its lowering effect on the intracranial pressure

mesure l'activité antidiurétique chez les cancéreux non cérébraux (BERNARD WEIL F., PIETTE C. & OLIVIER I. Action de la lysine vasopressine sur la concentration de la cellule en acides ribonucléiques. Étude sur des tumeurs cérébrales bénignes en survie. Pathol. Biol. sous presse 1968). Tout ici nous permettra peut-être de dire un jour que ce traitement hormonal, ou des traitements dérivés de ce traitement hormonal sont susceptibles d'agir sur l'évolutivité cancéreuse. Mais, en fait, tel qu'il est actuellement, c'est un traitement anti-œdémateux de la cellule saine et peut-être ce traitement a-t-il des pouvoirs plus importants mais nous n'en sommes pas encore sûrs.

CONCLUSION

M. Lindgren

This symposium was arranged to enable the presentation of a panorama of modern diagnostic procedures and of the therapy of intracranial glioblastoma multiforme. This tumour has a high incidence, grows fast, and, if left untreated has a gloomy prognosis. The specific aim was above all to find out whether improved diagnostic procedures can lead to the development of more effective therapeutic methods and to improvement of the prognosis.

ZULCH classified the biologic and morphologic aspects of this lesion. His proposal to devise and apply a uniform classification for brain tumours, to enable exact statistical comparison of different therapeutic methods, appears well founded. CRONQVIST described the difficulties encountered in the establishment of a differential roentgen diagnosis of vascular and avascular malignant gliomas and THERESE PLANIOL reported that gamma encephalography missed only 2 to 4 per cent of glioblastomas and that the nature of the lesion could usually also be determined.

The possibilities of diagnosing glioblastoma multiforme are today good, and further improvements as with the use of radio isotopes may soon be expected. But the possibilities of determining the exact extent of an intracranial glioblastoma multiforme are limited owing mainly to the invasive mode of growth of the tumour and to the frequently existing oedema. Knowledge of the extent of the neoplasm is, however, important for planning of both surgery and radiation therapy. Post mortem studies have taught us that the extent of the lesion is often underestimated. The dire consequences of such underestimation on radiotherapy have been described by KRAMER.

We know that some glioblastomas multiforme are moderately radiosensitive, although, unfortunately, the response is often only transient

In summary, the treatment of choice of intracranial glioblastoma multiforme still seems to be primary surgical decompression and removal of malignant tissue followed by adequate irradiation The results after combined neurosurgery and radiotherapy are better than after surgery alone Good palliation and some prolongation of life can be achieved, occasionally for a few years The degree of recovery after the combined treatment has been graded as good in many patients.

The treatment of glioblastoma multiforme, also the radiation treatment, will in a given case vary with the temperament, skill and experience of the surgeon and the radiotherapeutist A certain selection of candidates for treatment appears warranted Experience has shown the prognosis to be somewhat better for patients below 50 years without any appreciable mental involvement of paresis

Finally, I should like to thank all the members of the panel for their most valuable contributions and cooperation and the audience for all the questions that have promoted the discussion

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GASTRIC ULCERATION FOLLOWING COBALT TELETHERAPY

Estimation of the tolerance dose

by

B Sylven, K J Vikterlof and L B Schnurer

The risks of irreversible and clinically serious damage to various internal organs following external high-energy radiation therapy have increased at all clinics aiming at an effective cancericidal dose level. The conventional plans for the usual multi portal beams are liable to focus the attention on the supposed tumor region while the actual dose distribution to the surrounding healthy organs may be given less attention. The literature on such acute and chronic changes is now considerable and has recently been extensively reviewed (CADE 1966, gynecologic complications by FLETCHER et coll 1966, 1968). It would therefore appear desirable to obtain more accurate data on the tolerance limits of many organs.

This paper embodies an estimation of the tolerance dose of the stomach based on data from the literature and data from two new cases of gastric ulceration induced by irradiation. In addition microscopic features stressing a possible distinction between radiation induced and common ulcers are discussed.

Case reports

Case 1. A previously healthy, married woman, aged 38, had a large retroperitoneal tumor removed together with the left kidney. Microscopy disclosed a malignant neuroblastoma with marked central necrosis. Since the radical nature of the operation was questioned due to

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ach There were no metastases to lymph nodes or abdominal organs and recovery was uneventful

Histopathology Due to the larger dose of irradiation delivered in the first case the gastric changes induced were more marked and also appeared after a shorter time The wall thickness over the whole of the irradiated part of the stomach was estimated to be more than 2 cm in the fresh specimen and measured 1 5 cm after fixation in formaldehyde The upper non irradiated part presented on the other hand a completely normal texture The thickening was mainly due to massive edema the fluid being unusually rich in protein and fibrin which presented a picrinophilic staining reaction (Fig 2) No fibroplasia was present

The dramatic vascular changes included endarteritis fibrinoid necrosis of the vascular wall thrombosis and extensive interstitial haemorrhages (cf ENGELSTAD 1938 WARREN & FRIEDMAN 1942 and WOOD et coll 1963) The acute mucosal ulceration measured 2 5 cm in diameter and resulted from an almost complete necrotic desquamation of the lining this corresponds to a *picture clearly different from* the one seen in ordinary ulcer cases Other glandular cells remaining in the vicinity showed heavy irradiation damage of nuclear cytology cytoplasmic vacuolization and loss of secretory function (Figs 3 and 4) In addition many small mucosal *defects with overt haemorrhages* were present in other parts of the *irradiated* area These findings together indicate that the irradiation dose was far above the tolerance level

The histologic features were less distinctive in the *second case* Apart from *marked bulbar deformation* and scars due to previous small ulcers (cf roentgen examinations mentioned above and Fig 1) the operation specimen *disclosed* chronic gastro-duodenitis with considerable fibrosis and some *inflammatory* cell infiltration The mucosal lining was *thus intact at the time* of gastric resection

The first case thus presented a picture typical of radionecrosis in which *most parts* of the irradiated mucosa had lost its *regenerative power* The severe vascular and nuclear changes offered a clear cut distinction between radiation induced and simple ulceration (cf SELL & SKOV JENSEN 1966) The second case is of *greater interest* the prolonged course and the still retained tendency to healing of the mucosa suggest that the amount of irradiation *administered* was close to the tolerance dose

Estimation of the tolerance dose The tolerance dose can now be estimated within fairly narrow limits due to *the relatively fixed* position of the antrum and pyloric parts of *the stomach and* because of the generally *careful* treatment planning and dosimetry Previous data *on cases of* testicular tumors treated post operatively provide added support to the estimation Individual variations obviously exist and these may *amount to* some *10* per cent of the suggested



Fig 1 Condition repeatedly observed before gastric resection

capsular defects and firm adhesions to the aortic wall a course of postoperative irradiation was decided upon

A three portal telecobalt series was administered to the whole tissue volume corresponding to the original tumor and now partially occupied by the stomach The total dose to the distal half of the stomach was in excess of 5 500 rad/11 weeks The patient returned four months later with severe anemia haematemesis and melaena due to gastritis and edema of the distal half of the stomach wall directly corresponding to the field of irradiation *There* was in addition a large necrotic area of ulceration necessitating resection (the microscopic findings will be discussed in detail below) The patient unfortunately died after a few days with wound infection and haemorrhagic diathesis No tumor remnants were seen at autopsy and the remaining part of the stomach was normal

Case 2 Man aged 70 was operated for a seminoma on the left side Post operative opposing field cobalt irradiation was given to the para aortic and iliac lymph nodes The calculated total dose to the pyloric region was 4 200 ± 5 % rad/39 days

A short time after this treatment the patient developed constant dyspepsia Control roentgen examinations later disclosed marked gastritis and recurrent small areas of ulceration in the pyloric region (see Fig 1)

About 4 years later the patient still had persistent melaena and secondary anemia unresponsive to medical treatment which necessitated resection of the distal part of the stom

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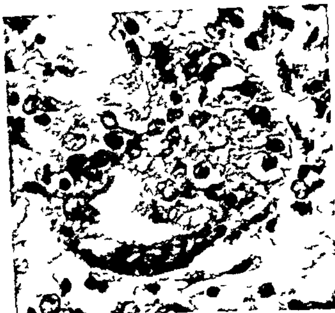


Fig. 4. Lethal cell damage with nuclear pyknosis, ballooning and vacuolization in the remaining cells. Normal mucin secretion abolished and no staining with the PAS, Alcian blue or HID Spicer techniques. × 640.

frequency of such changes can hardly be estimated and would appear to vary with age and previous gastric disorders.

If then the tolerance dose for fractionated high energy treatment is defined as the maximum dose not giving rise to acute or late gastric radionecrosis, it would appear safe not to exceed 4 300 ± 10 per cent rad/5 weeks. This agrees well with the 4 000 rad/5 weeks dose recommended by FRIEDMAN (1959) and SELL & SKOV JENSEN (1966), as well as by others. Recalculation of relevant doses given by different fractionation schemes is always difficult. The authors have used the approximation given by STRANDQVIST (1944) for their recalculations, assuming that with central doses of 150 to 200 rad such relations are widely used in clinical practice. A tolerance dose of this magnitude will apparently restrict the still higher dose levels sometimes desired in the treatment of upper abdominal tumors, doses that otherwise may be administered without any observable primary skin reactions with high-energy radiation. Moreover, it seems necessary to pay more attention in the future to the exact anatomical location of the antrum and the pyloric parts of the stomach during treatment planning.



Fig. 2. Acute ulceration with loss of the mucosal lining, inflammatory cell reaction, edema and haemorrhages. × 160.



Fig. 3. Epithelial radionecrosis and desquamation of cells in the pyloric glands away from the large ulcer. × 640.

tolerance dose. It must further be kept in mind that various kinds of trauma after irradiation may change the threshold figure (ENGELSTAD 1938).

Acute ulcers due to radiation necrosis of the sensitive mucous and submucosal layers have been reported at doses ranging from 4 300 rad/5 weeks (Case 1 of SELL & SKOV JENSEN), 4 600 rad/5 weeks (our Case 1, recalculated) and upwards to 4 800 to 4 900 rad/5 weeks. The risks apparently increase with a higher dosage (cf. BRICK 1955, and others) and the prospects of spontaneous healing will diminish. The frequency of ulceration would seem to become high at doses around and exceeding 5 000 rad/5 weeks, doses which are desirable and may even be exceeded in the treatment of lumbar node metastases from the more malignant and radioresistant testicular and other upper abdominal tumors.

Late ulcerations appearing years after irradiation are more difficult to evaluate as sequelae since they present less definite histologic changes and heal from time to time, as in our Case 2, which received a dose of about 4 000 rad/5 weeks. The

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TRIIODOTHYRONINE UPTAKE TEST IN GYNECOLOGIC RADIATION THERAPY

by

L LAAKSO T NIKKARI and M GRÖNROOS

The results of the triiodothyronine uptake test are influenced both by the amount of circulating thyroid hormones and by the availability of thyroxine binding proteins in plasma Changes in the uptake are thus caused either by agents affecting protein synthesis or by factors that alter directly or indirectly the function of the thyroid gland Whole body irradiation leads to decreased uptake in rats (HAHN 1967) Exogenous factors such as stress and drugs have been found to affect the values in man (SISSON 1965) The present authors were therefore interested in finding out whether gynecologic radiation therapy can alter these values especially as triiodothyronine is known to potentiate the radiation sensitivity of selected local tissues (GRIEM & STEIN 1960)

Material and Method The material comprised 13 women aged from 40 to 76 years who received radium and telecobalt therapy for genital carcinoma The first plasma sample was taken just before treatment and the second immediately after removal of the radium applicators The third sample was obtained in connection with the gynecologic examination at the end of telecobalt therapy The radiation doses given are presented in the Table

Submitted for publication 2 January 1969

SUMMARY

Two cases of gastric ulceration following external high energy irradiation are reported The vascular and cytologic changes in the mucosal cells made a distinction possible between irradiation induced and common ulcers The tolerance dose of the mucosa in the pyloric region may be estimated to about 4 300 ± 10 % rad given over 5 weeks

ZUSAMMENFASSUNG

Zwei Fälle von Magengeschwür nach äusserer Hochenergiebestrahlung werden mitgeteilt Die Gefäss und zytologischen Kern Veränderungen zeigten eindeutig den Unterschied zwischen Strahlen induzierten und gewöhnlichen Magengeschwüren Die Toleranzdosis der Magenschleimhaut im Pylorusgebiete wurde auf ungefähr 4 300 ± 10 % rad in 5 Wochen geschätzt

RÉSUMÉ

Présentation de deux cas d ulcération gastrique après irradiation externe avec un rayonnement de haute énergie Les lésions vasculaires et les lésions cytologiques des cellules de la muqueuse permettent de distinguer les ulcérations dues aux radiations et des ulcères communs La dose de tolérance de la muqueuse dans la région pylorique est estimée à environ 4 300 ± 10 % rad en 5 semaines

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Table

Diagnoses, age, radiation doses and triiodothyronine test values

Case	Diagnosis	Age	Radium therapy mgh		Tele cobalt rad	Triiodothyronine test		
			1st appl.	Total		Before treatment	After 1st appl.	After treatment
1	Ca corp. uteri gr. I	76	2750	5750	3600	27.1	29.0	26.1
2	Ca corp. uteri gr. I	56	3600	6300	3850	27.5	28.5	25.6
3	Ca cervicis ut. gr. I b	63	2940	6160	3850	28.9	33.4	31.9
4	Ca cervicis ut. gr. II b	47	3240	6920	3850	34.0	33.8	28.6
5	Ca cervicis gr. II a	65	3220	4900	3920	27.1	33.1	25.7
6	*Ca corp. ut. gr. II*	75	*3080*	*6080*	*3960*	*30.7*	*32.0*	29.5
7	Ca mammae I a Ca in situ portionis *St. post amp. uteri c. adnex.*	59	*2520*	*2520*	—	*31.5*	*36.0*	27.6
8	Ca in situ cervicis	43	1800	3300	—	24.0	25.8	19.5
9	Ca corp. ut. gr. III	49	3600	7500	3750	32.1	35.1	32.0
10	Ca in situ cervicis	60	3360	7140	—	26.5	30.4	28.4
11	Ca cervicis gr. I a	51	3360	6730	3750	28.2	36.5	26.8
12	Ca cervicis gr. II a	40	3960	7180	4550	31.1	37.[illegible]	30.3
13	Ca cervicis gr. III	67	3200	3200	5400	30.9	—	27.0
					Mean	29.2	32.5	27.6
					SD	±2.8	±3.5	±3.4

The triiodothyronine resin uptake test was performed according to WOLDRING et coll. (1961), except that triiodothyronine labelled with ^{125}I (Radiochemical Centre, Amersham, England) was used. All the samples from the same patient were examined simultaneously. Student's t test was applied for evaluation of the significance of differences between paired observations.

Results

The results are given in the Table. There is a small but significant ($P < 0.001$) increase (difference $\pm$ SD $= +3.4 \pm 2.6$) in the triiodothyronine uptake following radium application. This is followed by a significant ($P < 0.001$) decrease (-4.8 ± 2.8) to values (27.6 ± 3.4) significantly lower ($P < 0.05$) than those before therapy (29.2 ± 2.8). These results indicate that gynecologic radiation therapy can cause changes in the triiodothyronine uptake: an initial rapid increase is followed by a post-treatment decrease to values lower than the original

Discussion

Several mechanisms may be responsible for the changes observed in the triiodothyronine uptake test during gynecologic radiation therapy. The direct effect of radiotherapy on the thyroid gland hardly ever enters into the question as the amount of scatter radiation received by this gland in the treatment of genital carcinoma is fairly small. As no PBI values were available it is difficult to say whether the changes that occurred were in the amount of circulating hormones or in the thyroxine binding proteins. It is possible that while blood circulates in the organs given irradiation the structure of the plasma proteins changes and the thyroid hormone binding capacity decreases. This could be the reason for the elevation of the triiodothyronine uptake observed during treatment.

The increase may on the other hand be due to acute stress caused by the application of radium which leads to an increase in the production of ACTH and also that of TSH in the pituitary gland (HARRIS 1955). This explanation would seem to be in agreement with earlier observations (GRONROOS & KAUPPILA 1959, SOIVA et coll. 1959) in test animals that increased gonadal function in acute stress and decreased function in prolonged stress may be attributable to changed production of gonadotrophins by the anterior lobe of the hypophysis. If the release of TSH is correlated with gonadotrophin production, the latter mechanism also explains the decrease in triiodothyronine uptake after radiotherapy to below the pre-therapeutic level. However, the decrease appears to be so slight as to be of any significance in the metabolism and for the therapeutic results.

SUMMARY

Gynecologic radiation therapy may cause small changes in the triiodothyronine uptake. An initial significant increase is followed by a significant decrease to values lower than those before therapy. The reason for this and the significance of the changes are discussed.

ZUSAMMENFASSUNG

Gynäkologische Strahlenbehandlung kann kleine Veränderungen in der Aufnahme von Triiodothyronin verursachen. Zuerst erfolgt eine signifikante Zunahme und dann eine starke Abnahme bis zu Werten, die niedriger sind als die bevor der Bestrahlung. Die Ursache und die Bedeutung dieser Erscheinungen werden besprochen.

RÉSUMÉ

Le traitement de lésions gynécologiques par les radiations peut causer de petites modifications dans la fixation de la triiodothyronine. Cette fixation augmente d'abord de façon importante jusqu'à des valeurs inférieures à celles qui existaient avant le traitement. Les auteurs examinent les raisons et l'intérêt de ces modifications.

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FROM THE DEPARTMENT OF GYNECOLOGY THE CLINIC OF RADIOTHERAPY KING GUSTAF V JUBILEE CLINIC SAHLGRENSKA SJUKHUSET, GOTHENBURG SWEDEN

MYOMETRIAL BLOOD FLOW STUDIES IN CARCINOMA OF THE CORPUS UTERI

A preliminary report on the clearance method using xenon 133

by

CLINTON NYSTROM LARS FORSSMAN and BENGT ROOS

The local isotope clearance method for determination of the regional blood flow was originally described by KETY (1949) and the technique has recently been applied to the study of disorders of the peripheral circulation with freely diffusible inert indicators such as xenon 133 and krypton 85 The isotope clearance method has become part of the routine investigation of arterial occlusive diseases of the legs (TØNNESEN 1965)

The blood flow of the human myometrium has also been studied with this technique Interest has been directed mainly towards normal and abnormal pregnancies GUILHEM et coll 1963 1966 LYSGAARD & LEFEVRE 1965 MUNCK et coll 1964) The regional blood flow in the myometrium during pregnancy has been shown to be about 9 ml/min/100 g at sites remote from the placenta and about 23 ml min 100 g in its vicinity (*FALK et coll 1966* JANSON 1966)

A pilot study was performed in a small series of tumor cases in order to study myometrial blood flow in non pregnant conditions These were chosen because it was believed that extreme variations in blood flow might be recorded

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Table 1

Case material and estimations of the blood flow in twelve cases of carcinoma of the corpus uteri

Case No	Age	Deliveries abortions extrauterine pregnancies	Meno pause	Uterine depth	Remarks	Tumor differ entiation	MyBf/Xe (ml/min 100 g)	
							Cervix	Corpus
96 09 04	70	0—0—0	1950	7 5	—	High	15	1 3
91 06 14	75	0—0—0	1941	7 5	—	High	9 3	[illegible]
09 07 26	57	4—2—0	1964	8 5	—	High	[illegible]	24[illegible]
08 09 04	58	2—0—0	1964	9	Estrogen treatment	High	37 4	[illegible]
10 10 04	56	2—0—0	1965	8 5	—	High	2[illegible]	9
10 0[illegible] 26	56	1—1—0	1954	6 5	—	Low	15 1	34
07 03 29	59	0—0—0	1960	6 5	—	Low	27	40.5
93 02 06	73	4—0—0	1943	7	Depth of injection uncertain	Low	—	10 8
19 03 10	47	0—0—0	—	6	—	Low	27	60 [illegible]
08 10 23	58	0—0—0	1960	9	Treatment with linear accelerator before present measurements	Low	10 1	3[illegible] 3
14 05 18	52	4—0—0	—	12	—	High	27	18 [illegible]
06 04 22	60	4—1—0	1959	8	—	Low	—	69

Method Xenon 133 dissolved in sterile 0 9 % saline was injected into the cervix uteri with a small calibre needle This was passed 1 cm into the cervical tissue parallel to and at a distance of about 7 to 10 mm away from the cervical canal The injection into the fundus myometrium was made through a special cannula allowing control of the depth of injection About 50 μCi were injected at either site Great care was taken not to inject any gas bubbles and no aspiration was made prior to the injection The injection was performed slowly and the needle was left in situ for 15 to 20 seconds before withdrawal No anaesthesia was used

The patient was placed in the lithotomy position with a scintillation detector above the symphysis pubis The collimator was adjusted so that the crystal would cover the true pelvis A multichannel analyzer was used, the number of impulses per unit time was recorded The time interval was altered during the investigation and one tenth of a minute was found to be a suitable unit The recorded values

were plotted on semi logarithmic paper from which the half time ($t_{\frac{1}{2}}$) was calculated

The regional blood flow (MyBf) was then calculated from the formula

$$MyBf = \frac{\log^e 2}{t_{\frac{1}{2}}} \lambda \; 100 \qquad (1)$$

in which λ is the partition coefficient tissue/blood for xenon The partition coefficient for skeletal muscle was used in the calculation (CONN 1961)

Radiation doses The calculation was made according to the following equation

$$X = B \frac{G \; A}{r^2} e^{-\mu R/h} \qquad (2)$$

where B is the build up factor A the activity in mCi r the distance in cm μ the total absorption coefficient in cm[1] G the specific gamma constant for which the value of 0 44 R cm /mCi h was used and X is the rate of exposure in R/hour

The absorption of the primary radiation and the contribution from the secondary radiation were neglected These are equivalent to $Be^{-\mu r} = 1$ These two effects partly but not completely, counteract each other, the absorbtion dominating somewhat The contribution from the activity under transport in the blood away from the site of injection has also been neglected as there are no reliable data concerning the volume of the blood vessels and the velocity of the blood This contribution is however probably considerably smaller than the radiation from the site of injection The values 6 5 and 5 5 cm were used for the distance r from the cervix and the fundus respectively This gives

$$X_{cervix} = \frac{0\;44 \quad 0\;05}{6\;5^2} \; 10^3 = 0\;52 \text{ mR/h}$$

$$X_{fundus} = \frac{0\;44 \quad 0\;05}{5\;5^2} \; 10^3 = 0\;73 \text{ m/Rh}$$

The maximal half times observed after an injection of 50 μCi xenon 133 were 7 minutes in the cervix and 40 minutes in the corpus Multiplication by these times gives the maximal gonadal radiation exposures of (1) 0 06 mR from injection in the cervix and (2) 0 49 mR from injection in the corpus The unit R (roentgen) in these approximative calculations may be considered equal to the unit rad

Material Twelve cases of carcinoma of the corpus uteri were studied the measurements always being made prior to the radium treatment External

Table 2

Statistical analysis and comparisons of blood flow in relation to tumor differentiation in twelve cases of carcinoma of the corpus uteri

	Low differentiated tumors	High differentiated tumors
Mean age	58.8±3.4	61.3±3.7
Cervical blood flow (ml/100 g/min)	19.8±4.3	20.5±4.3
Corpus blood flow (ml/100 g/min)	41.2±8.6*	10.3±3.8*

* *Difference statistically significant t = 3.3. The table of t distribution gives t = 3.2 for 10* degrees of freedom and $p < 0.05$

therapy with the linear accelerator was however in one case started before the study. The ages of the patients lay between 47 and 75 years. The cases are briefly described in Table 1.

There was no statistically significant difference between the mean age of the two groups nor between these as indicated by the cervical blood flow. There was however a statistically significant difference according to the t test between the mean values of the corpus blood flow. The estimations are presented in Table 1 and the statistical analyses in Table 2 giving the mean values ± standard errors of the mean.

Measurements of the regional blood flow under pathologic conditions in the uterus have up till now not been performed with the xenon clearance method.

The technique was varied during the study but the depth of the injection was always the same. The calibre of the special cannula was reduced in order to minimize tissue trauma and the risk of reflux along the needle tract. The tumor histology varied between very highly differentiated and anaplastic carcinomas. The uterine depth was between 6 and 12 cm but it was not possible to relate the variations in blood flow in the cervix myometrium with the type of tumor, or the uterine depth, the mean value lying between the values reported by Munck et coll. (1964) in the cervix and isthmus of the non pregnant uterus. The lowest value was recorded in an elderly woman who had a highly differentiated tumor, and the greatest value in a post menopausal woman with a highly differentiated neoplasm that had received estrogen therapy prior to measurement.

It was possible to relate the variations of the blood flow in the fundus myo-

metrium to the histologic differentiation of the growth The mean blood flow was 10 3 ml/min/100 g with a range from 1 2 to 24 2 ml/min/100 g in six cases of highly differentiated tumors Six cases of low tumor differentiation had a mean blood flow of 41 2 ml/min/100 g the range being from 10 8 to 69

The group investigated is quite small Although the technique was varied in some respects this cannot account for the changes in blood flow that seem to be related to the histologic features of the tumors Alterations in the partition coefficient tissue/blood for xenon may represent a factor that contributed to the variations observed and therefore clearly require further study The haemoglobin content of the blood may affect the partition coefficient (Conn 1961) but in the group studied the variations in the haemoglobin values were not of sufficient magnitude to account for the variations observed in the xenon clearance

It has not been possible to relate the xenon clearance to the uterine depth It may be that the variations in the blood flow may indirectly reflect the fluctuating intracellular metabolism which in turn is related to the histologic characteristics of the neoplasms

The investigation has indicated that the xenon clearance method is simple to apply to the myometrium during non pregnant conditions as well The radiation doses are small and studies in the same patient may easily be repeated

SUMMARY

The myometrial blood flow was investigated in twelve cases of carcinoma *of the corpus* uteri with the xenon 133 clearance method A statistically significant difference between low and high differentiated neoplasms depending on the blood flow in the fundus myometrium was *recorded*

ZUSAMMENFASSUNG

Die Durchblutung des Myometriums wurde mittels der *Xenon 133 Methode* in zwolf Fallen von Carcinom des Corpus uteri gemessen Eine *statistisch* signifikante Differenz konnte zwischen Carcinomen von niedriger bzw hoher Differenzierung nachgewiesen werden

RÉSUMÉ

Les auteurs ont étudie le debit sanguin du *myometre* dans douze cas de cancer du corps utérin par la méthode de clearance du *xénon 133 Ils ont* trouve une difference statistique significative entre les cancers peu differenciés *et les cancers* tres differencies difference dépendant du debit sanguin dans le myometre du fond de l uterus

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SIGNIFICANT FACTORS IN RED CELL MASS CHANGES AFTER FRACTIONATED LOCAL RADIOTHERAPY

by

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Recently (Levitt et coll 1965) reported the results of serial studies of plasma volume and red cell mass measured simultaneously with ^{1}Cr and $^{1\ 5}$I employing the method of Wood & Levitt (1965) Thirty patients 16 males and 14 females undergoing local fractionated irradiation for malignant disease were examined in this manner Sixteen received irradiation to the thorax nine to the pelvis and six to the head and neck In seven of the thirty patients we found a decrease in red cell mass during radiation therapy with a subsequent rise one month after completion of the treatment There was a concomitant increase in plasma volume during the treatment and a subsequent drop after treatment was completed This phenomenon seemed to occur most frequently in patients treated for carcinoma of the lung (three of nine) and those treated with large fields (three of eight) or in patients receiving irradiation to the thorax (five of six)

Such studies have now been carried out in a further thirty patients The findings in the first group and the later one have been combined and the values obtained have been studied to determine the statistical significance of the observed changes and to determine the significant factors

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Material and Method. Sixty cases, 36 males and 24 females, were treated by either a 2 MV Van de Graaf or a Theratron 80 cobalt 60 unit. The sites of the neoplastic disease treated were as follows:

Carcinoma of the lung	22
Carcinoma of the breast	13
Carcinoma of the cervix	6
Carcinoma of the oral cavity and oropharynx	11
Carcinoma of the bladder	3
Carcinoma of the brain	3
Carcinoma of the ovary	1
Carcinoma of the gastrointestinal tract	1

The age ranged from 25 to 85 years with an average of 55.

The parameters studied were venous hematocrit, computed hematocrit, RBC mass, plasma volume, total blood volume and estimated blood volume. The plasma volume and red cell mass were determined simultaneously using ^{51}Cr and ^{131}I as previously described (WOOD & LEVITT 1965). The estimated blood volumes were calculated by the method of NADLER et coll. (1962).

These investigations were made before, at the mid point, at the end and one month after completion of radiation therapy, and an attempt was made to have all these studies completed in all the cases. This was accomplished in the majority of cases but not in all due to technical difficulties.

For statistical purposes, the means of the above parameters were further categorized on the basis of site treated, field size, and tumor dose. The sites of treatment were separated into 'head and neck', 'chest', and 'pelvis'. The field sizes were divided into categories of less than 150 cm^2, 150 to 300 cm^2, and more than 300 cm. The total tumor doses were divided into categories of less than 5 000 rad, 5 000 to 6 000 rad and over 6 000 rad.

The significance of field size, site treated and tumor dose upon the means of the parameters studied was evaluated by computation of the standard error (S. E.) for the mean value of visit 1, and the 95 % confidence limit (0.95 CL) for this same mean value. The means for visits 2, 3 and 4 were then examined to see if they were included in the 0.95 CL. If not, the difference was considered statistically significant at $p < 0.05$.

Results

Site treated. The RBC mass was found to decrease significantly at the end of treatment in patients having the chest treated. There was a subsequent rise one month post therapy although the mean remained significantly lower than the initial level (Table 1).

Table 1

Red cell mass values on different occasions in relation to the site of irradiation therapy

Site treated	Visit	1	2	3	4
Pelvis	N	11	9	11	9
	Mean	1322	1346	1215	1338
	S E	86 5			
	0 95 CL	1129—1515			
Chest and mediastinum	N	35	31	35	25
	Mean	1620	1609	1380*	1421
	S E	60 4			
	0 95 CL	1497—1743			
Head and neck	N	13	12	12	10
	Mean	1664	1840	1733	1 61
	S E	113 1			
	0 95 CL	1417—1911			

* Denotes that this mean is significantly different from visit 1 at $p < 0\ 05$ all other comparisons are not significant

Plasma volume, venous hematocrit and estimated blood volume did not show a significant variation with the site of irradiation The total blood volumes and computed (isotope) hematocrit showed a significant variation at the end of therapy in patients who had mediastinum and breast irradiated This is explained by the change in red cell mass

Tumor dose There was a significant decrease in red cell mass at the end of treatment and subsequent rise one month post treatment in patients treated to tumor doses of less than 5 000 rad and 5 000 to 5 999 rad but not in the group receiving 6 000 rad or more There was no significant variation in plasma volume venous hematocrit or estimated blood volume related to tumor dose (Table 2)

Field size There was a significant drop in red cell mass at the completion of therapy in patients receiving irradiation to field sizes of 150 to 300 cm There was no significant change in patients whose fields were less than 150 cm or over 300 cm (Table 3)

Further analysis In view of the findings of the significant drop in red cell mass in patients receiving irradiation to the breast and chest fields it was felt that the significant factor in red cell mass change was that of irradiation of the

Table 2

Red cell mass values on different occasions in patients receiving different irradiation doses

Range rad	Visit	1	2	3	4
3 000—4 999	N	13	11	12	16
	Mean	1562	1534	1263*	1405
	S E	110			
	0 95 CI	1322—1802			
5 000—5 999	N	18	16	16	13
	Mean	1465	1488	1271*	1410
	S E	78 5			
	0 95 CI	1299—1631			
6 000 or more	N	29	22	27	[illegible]
	Mean	1660	1780	1574	1616
	S E	72 5			
	0 95 CI	1511—1809			

* Denotes that this mean is significantly different from visit 1 at $p < 0.05$ all other comparisons are not significant

Table 3

Red cell mass values on different occasions in relation to field sizes irradiated

	Visit	1	2	3	4
150 cm^2 or less	N	17	15	16	15
	Mean	1650	1772	1636	1673
	S E	93			
	0 95 CI	1453—1847			
151—299 cm^2	N	28	23	28	20
	Mean	1578	1627	1351*	1391*
	S E	72			
	0 95 CI	1430—1726			
300 cm^2 or over	N	15	15	15	[illegible]
	Mean	1452	1394	1295	1461
	S E	78			
	0 95 CL	1295—1619			

* *Denotes that this mean is significantly different from visit 1 at $p < 0.05$ all other comparisons are not significant*

Table 4

Red cell mass values on different occasions in relation to field sizes in patients receiving mediastinal therapy only

	Visit	1	2	3	4
Less than 150 cm	N	11	10	11	8
	Mean	1439	1345	1290	1374
	S E	96			
	0 95 CL	1275—1603			
150—300 cm	N	20	17	15	20
	Mean	1751	1786	1425*	1464*
	S E	18 5			
	0 95 CL	1587—1915			

* Denotes that this mean is significantly different from visit 1 at $p < 0.05$ all other comparisons are not significant

chest wall the mediastinum or both To test this hypothesis and further evaluate the effect of field size and dose on the chest wall statistical studies were carried out on all patients receiving chest wall irradiation in which the consideration of only the dose to the thorax and only the size of the thoracic field irradiated were evaluated

Size of thoracic field Field sizes of less than 150 cm and 151 cm to 300 cm were evaluated Because of the small number of cases fields larger than 300 cm could not be adequately evaluated There was a significant drop in red cell mass at the end of therapy in patients with field sizes between 150 to 300 cm (Table 4)

Thoracic tumor dose There was a significant decrease in red cell mass at the completion of therapy or one month later in all groups divided on a basis of dose to the thorax (Table 5) There was no significant change in plasma volume or total blood volume in these patients

Discussion

Our previous study (LEVITT et coll 1965) demonstrated that there appeared to be a decrease in red cell mass following local irradiation in certain patients who were treated for carcinoma of the lung and had large multiple areas treated or who had thoracic irradiation

The present study has demonstrated that the changes in red cell mass are of

Table 2

Red cell mass values on different occasions in patients receiving different irradiation doses

Range rad	Visit	1	2	3	4
3 000—4 999	N	13	11	12	16
	Mean	1562	1534	1263*	1405
	S E	110			
	0.95 CI	1322—1802			
5 000—5 999	N	18	16	16	13
	Mean	1465	1488	1271*	1410
	S E	78.5			
	0.95 CI	1299—1631			
6 000 or more	N	29	22	27	20
	Mean	1660	1780	1574	1616
	S E	72.5			
	0.95 CI	1511—1809			

* Denotes that this mean is significantly different from visit 1 at $p < 0.05$ all other comparisons are not significant

Table 3

Red cell mass values on different occasions in relation to field sizes irradiated

	Visit	1	2	3	4
150 cm² or less	N	17	15	16	15
	Mean	1650	1772	1636	1673
	S E	93			
	0.95 CI	1453—1847			
151—299 cm²	N	28	23	28	20
	Mean	1578	1627	1351*	1391*
	S E	72			
	0.95 CI	1430—1726			
300 cm² or over	N	15	13	15	12
	Mean	1452	1394	1295	1461
	S E	78			
	0.95 CL	1295—1619			

* Denotes that this mean is significantly different from visit 1 at $p < 0.05$ all other comparisons are not significant

of the blood producing bone marrow of the sternum vertebra and ribs since the ribs bone marrow and vertebrae make up a great percentage of the blood producing marrow in patients in the cancer age range (WINTROBE 1961) GOSWITZ s report (GOSWITZ et coll 1963) on serial bone marrow studies in patients receiving portal irradiation tends to confirm this hypothesis (Two of these patients received thoracic irradiation) A definite decrease in red cells precursors and the more immature granulocyte was noted at approximately midpoint of therapy This finding of localized bone marrow depression (without a decrease in red cell count) following localized irradiation has been confirmed by other investigators (HUTAFF & BELDING KORNBLUM et coll STEWART & DISCHE SYKES et coll)

Our findings that patients receiving thoracic irradiation had significant red cell mass changes regardless of dose probably can be accounted for by the fact that all doses were 3 000 rad or more SYKES et coll have demonstrated that the sternal marrow is depressed and usually does not regenerate in patients receiving 3 000 rad or more Although we made no bone marrow studies in these patients it is reasonable to assume a similar event in our patients In this regard it is interesting to note that when all patients receiving a dose of 6 000 rad are considered there are no significant red cell mass changes whereas when patients receiving mediastinal irradiation to 6 000 rad are considered separately there is a significant change This is most likely explained by the fact that most of the patients receiving irradiation to this dose were treated to the head and neck or pelvis

Another possible cause in the decrease in red cell mass may be the effect of irradiation on the capillaries of the lung It has been shown that increased capillary permeability follows total body irradiation due to capillary wall damage (FUNDENBERG et coll 1961 KAHN & FURTH 1952 ROSS et coll 1952 SZABO et coll 1958 WISH et coll 1952) It is conceivable that this increased capillary permeability would account for some part of the change in red cell mass in view of the large numbers of capillary spaces in the lung

This change in the red cell mass does not appear to be due to an abscopal effect since it was not found to be significant with pelvic or head and neck irradiations Further the change in red cell mass does not appear to be related to the course of the disease in that there is an increase in red cell mass after completion of therapy

Conclusion

A significant decrease in red cell mass at the completion of fractionated local irradiation to the thorax was observed This change does not seem to be related to dose since it was significant in all patients receiving thoracic irradiation at

Table 5

Red cell mass values on different occasions in relation to the doses given in patients receiving mediastinal therapy only

Range rad	Visit	1	2	3	4
3 000—4 999	N	10	6	8	6
	Mean	1640	1765	1926*	1376
	S E	140			
	0 95 CL	1324—1956			
5 000—5 999	N	14	13	14	10
	Mean	1474	1469	1259*	1371
	S E	84			
	0 95 CL	1293—1655			
Over 6 000	N	11	9	10	7
	Mean	1862	1770	1661	1580*
	S E	90			
	0 95 CL	1616—2063			

* Denotes that this mean is significantly different from visit 1 at $p<0.05$ all other comparisons are *not significant*

a significant nature and are related to thoracic irradiation and fields of at least *150 cm to 300 cm in size The change in red cell mass appears to be related* to the total field size of the thorax irradiated but does not appear to be related *to the dose*

Previous work suggested that local fractionated irradiation does not significantly affect peripheral red cell counts (COSWITZ et coll 1963, HUTAFF & BELDING 1955, JACOBSON & MARKS 1947 KORNBLUM et coll 1938, MOSSBERG 1943 STEWART & DISCHE 1956, SYKES et coll 1960) This change in the red cell mass has probably not been shown in these previous studies because of the methods of measurement used, i e hematocrit, hemoglobin, and red cell count do not accurately reflect the true red cell mass BERLIN, and others (BERLIN et coll 1952, 1955, DENSTED 1943, FUNDENBERG et coll 1961 GREGERSON & RAWSON 1959) have demonstrated the inaccuracies in evaluating the red cell mass by the use of any method other than the measurement of the actual red cell mass The necessity of evaluating the red cell mass and plasma volume by separate techniques has again been demonstrated in this study, as has the possibility of error involved in calculating the red cell mass or plasma volume by estimation rather than by direct measurement

The most likely mechanism for decrease in red cell mass is the depression

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the three dose levels evaluated The change may be related to the total area of the thorax irradiated since it was not significant in fields smaller than 150 cm Assuming that the data represent normal distribution and the observations were independent, these findings would represent significant changes, with a probability level of less than 0 5 that they are associated by chance

SUMMARY

In sixty patients treated with fractionated local irradiation to the head and neck thorax and pelvis serial studies with determination of the venous hematocrit computed hematocrit red cell mass plasma volume total blood volume and estimated blood volume were performed A significant decrease in red cell mass during treatment apparently due to irradiation was only noted in patients receiving thoracic irradiation This was related to field size but not to dose The possible reasons for this phenomenon are discussed

ZUSAMMENFASSUNG

In 60 Patienten die mit fraktionierter lokaler Bestrahlung von Kopf Hals Thorax und Becken behandelt wurden wurde eine Reihe von Studien vorgenommen in denen der venöse Hämatokrit und der berechnete Hämatokrit die Menge der Erythrocyten das Plasmavolumen und das totale sowie berechnete Blutvolumen festgestellt wurden Eine signifikante Abnahme der Erythrocytenmenge wurde nur in denjenigen Patienten observiert die Strahlenbehandlung des Thorax erhielten Die Abnahme war mit der Feldgrosse aber nicht mit der Dosis verbunden Die Ursache des Auftretens dieses Phänomen wird diskutiert

RÉSUMÉ

Les auteurs ont fait des examens en série de l'hématocrite veineux de l'hématocrite calculée de la masse des erythrocytes du volume plasmatique et du volume sanguin total chez 60 malades traités par irradiation locale fractionnée de la tete et du cou du thorax et du bassin Ils n'ont constaté une diminution significative de la masse érythrocytaire au cours du traitement apparemment sous l'effet de l'irradiation que chez les malades soumis à une irradiation thoracique Cette diminution est en rapport avec la dimension du champ mais non avec la dose Les auteurs discutent les raisons possibles de ces phénomènes

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Table 1

Blood counts in poisoned mice and in control mice

	$HgCl_2$	Controls	P
Hgb	10 9 grampercent	15 5 grampercent	<0 001
Er	6 5 millions/mm	9 6 millions/mm	<0 001
MCHC	33 percent	32 percent	
Hcr	34 percent	46 percent	<0 001
Leuc	2550/mm	2122/mm	

Table 2

Effect of roentgen irradiation on the cobalt accumulating capacity of mouse kidney

Kidney	Weight of kidney mg	Cpm/mg of kidney tissue	Cpm/whole kidney	P
Irradiated	69	4291	295663	<0 001
Intact	216	4187	903641	<0 001

Table 3

Effect of HgCl treatment on the cobalt accumulating capacity of mouse kidney

Animal	Weight of kidney mg	Cpm/mg of kidney tissue	Cpm/whole kidney	P
Treated	216	103	27605	<0 001
Control	270	162	35073	<0 001

localized in the renal tubular cells both in healthy and diseased kidneys the latter accumulated considerably less activity than normal kidneys The amount of radioactivity retained by the cortex of normal kidneys was appreciably greater than the amount retained in the medulla

The present study was undertaken in an attempt to reproduce in experimental animals the effects observed in human patients

Material and Methods The experimental material consisted of 200 young white mice of inbred strain Two kinds of kidney damage were produced 1) irradiation nephritis and (2) chronic nephritis by poisoning with corrosive sublimate (mercuric bichloride HgCl)

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RETENTION OF COBALT IN EXPERIMENTALLY INDUCED KIDNEY DISEASE

Studies of ^{60}Co in irradiated and sublimate-poisoned mouse kidney

by

HEIKKI A SALMI and ILMARI LINDGREN

The inorganic cobalt ion has been considered important in renal erythropoietin production (JACOBSON et coll 1960) and has been shown to have a curative effect in treating human renal anemia (GARDNER 1953, KASANEN et coll 1962, 1963) *This effect has been assumed in conjunction with the hypothesis* that inorganic cobalt stimulates the synthesis of the humoral erythropoietic agent (JACOBSON et coll) A low erythropoietin level has been demonstrated in patients with renal anemia (GOLDWASSER et coll 1958, JACOBSON et coll) Slight or no erythropoietic activity has been reported in urine from anemic and uremic patients (FINNE 1968) The retention of radioactive ^{60}Co has been studied in normal and glomerulonephritic human kidney tissue a clear cut *difference* was observed (LINDGREN & SALMI 1968) In normal kidneys, ^{60}Co was localized in the renal cortex close to the corticomedullar margin

Autoradiographically the glomerulonephritic kidneys also presented activity in the cortex this occurred in irregular paths, however, and occasional large areas in the corticomedullary region were without activity Radioactive ^{60}Co was

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Fig 2 Autoradiogram of the kidney of a mouse treated with corrosive sublimate until anemia developed A small amount of ^{60}Co has accumulated in the renal cortex ×25

In both experimental series the animals were sacrificed 24 hours after the isotope injection A control series that received only the radioactive cobalt chloride was also maintained Blood counts were made on both the experimental and control series (Table 1) Histologic specimens were obtained of the $HgCl_2$ series in order to exclude the possibility of toxic effects on the bone marrow The marrow from the femura and vertebrae disclosed microscopically normal active hemopoiesis in all the cell lines

The stripping film technique with Kodak AR 10 and AR 50 films was employed for autoradiography The standard alcohol xylol technique was used in preparation of the histologic samples This technique washes out water soluble ions the remaining ^{60}Co being definitely protein bound

The tissue specimens were digested in sulpuric acid and the radioactivity was measured in a well type scintillation counter

Results

Autoradiography revealed that the greatest activity in normal mouse kidney is concentrated near the corticomedullary zone with wedge shaped areas towards



Fig 1 Autoradiogram of the kidney of a control mouse Activity of ^{60}Co most abundant at the corticomedullary boundary ×25

In irradiation nephritis, one kidney was removed and the remaining kidney was lifted from its bed so that it would receive strictly local irradiation, the latter thus remained attached by its pedicle, through which the circulation continued The radiation was administered unilaterally, in order to minimize the radiation dose, the mobilized kidney being placed on a 5 mm lead sheet to avoid the effects of total body irradiation Doses varying from 3 000 to 4 000 R were delivered by a Machlett roentgen tube at 50 kV The cobalt chloride isotope ($^{60}CoCl_2$, specific activity 50 6 μCi μg Amersham, England) in a dose of 0 6 mCi was administered after 21 days

Chronic nephritis was produced by injecting another series of test animals intramuscularly with daily doses of $HgCl_2$ 2 % in normal saline solution Progressive doses were given starting with 0 1 ml on the first day, with an additional 0 1 ml daily until half the number of test mice had died This occurred at the forty third day at this time the surviving animals were also given the cobalt chloride isotope



Fig 4 Roentgenogram from the kidney of a mouse after open irradiation of the kidney with 4 000 R The kidney is shrunken and the accumulation of ^{60}Co in the tubular cells is diminished (The arrow indicates the direction of the radiation beam.)

kidneys the smaller total accumulation probably being due to the shrinkage of the radiated kidney

It is obvious that corrosive sublimate destroys a great number of the tubuli as evidenced by high resolution autoradiography The tubular damage prevents the storing of cobalt in the renal cortex The animals develop normochromic anemia with intact bone marrows the anemia is probably renal in nature and is possibly due to the lack or decrease in the synthesis of renal erythropoietin The present results indirectly suggest that the site of synthesis of renal erythropoietin may be the tubular cells

Acknowledgements

This work was supported by grants from the National Research Council for Medical Sciences and the Sigrid Juselius Foundation H.A.S worked during the investigation as Junior Fellow of the National Research Council for Medical Sciences

SUMMARY

The accumulation of ^{60}Co in experimentally damaged mouse kidney was studied by means of autoradiography and scintillometry the damage being induced either by corrosive sublimate poisoning or by open roentgen irradiation. The radioactivity accumulated in the

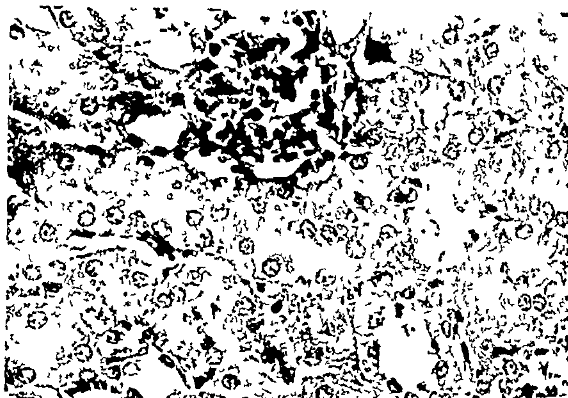


Fig 3 Detail of the kidney in fig 2 The glomerulus is well preserved but the tubular cells bear evidence of albuminous degeneration the cytoplasm is swollen and granular Van Gieson stain ×400

the renal capsule Activity was absent in the medulla or in the blood vessels near the boundary between the cortex and the medulla High resolution autoradiography demonstrated that most of the activity was in the tubuli, and that there was none in the glomeruli

In the diseased kidneys both in the irradiated and in those affected by the corrosive sublimate, the radioactive cobalt lay in scattered irregular paths in the cortex The scintillometric measurements (Tables 2 and 3) indicated that a diseased kidney accumulated a smaller amount of cobalt in the cortex than a normal kidney These measurements confirmed the impression given by the autoradiographic appearances

The present results, with experimentally induced renal disease are similar to those arrived at in human subjects dying of chronic glomerulonephritis (LINDGREN & SALMI 1968)

The irradiated kidney accumulates considerably less cobalt than the intact kidney (Table 2) However, the activity per tissue weight unit is similar in both



Fig 4 Roentgenogram from the kidney of a mouse after open irradiation of the kidney with 4 000 R. The kidney is shrunken and the accumulation of 60Co in the tubular cells is diminished (The arrow indicates the direction of the radiation beam)

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SUMMARY

The accumulation of 60Co in experimentally damaged mouse kidney was studied by means of autoradiography and scintillometry the damage being induced either by corrosive sublimate poisoning or by open roentgen irradiation The radioactivity accumulated in the

tubular cells of the cortex both in the diseased and healthy kidneys. The role of cobalt in renal anemia and the production of erythropoietin are discussed.

ZUSAMMENFASSUNG

Die Anreicherung von ^{60}Co in experimentell beschädigten Mausenieren wurde mittels Autoradiographie und Szintillometrie studiert. Die Nierenschädigung wurde mittels Verabreichung von *Sublimat oder mittels offener Röntgenbestrahlung* herbeigeführt. Die Anreicherung der Radioaktivität fand in den tubulären Zellen des Cortex sowohl in den gesunden als auch in den geschädigten Nieren statt. Die Rolle des Cobalts in renaler Anämie und in der Produktion von Erythropoietin wird erörtert.

RÉSUMÉ

Les auteurs ont étudié sur des souris par autoradiographie et par scintillométrie la fixation de ^{60}Co sur les reins lésés expérimentalement, la lésion étant produite soit par un empoisonnement par le sublimé corrosif soit par une irradiation directe par les rayons de roentgen. La radioactivité s'accumule dans les cellules tubulaires du cortex aussi bien dans les reins lésés que dans les reins sains. Les auteurs étudient le rôle du cobalt dans l'anémie rénale et dans la production d'erythropoïétine.

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FROM THE LABORATORY OF RADIOPATHOLOGY (PROF. H. B. LAMBERTS), THE STATE UNIVERSITY, GRONINGEN, THE NETHERLANDS

RADIATION INDUCED RELEASE OF CATECHOLAMINES FROM PERFUSED BOVINE ADRENAL GLAND

by

ZIVAN DEANOVIC and TJEERD S. VENINGA

A decrease in the catecholamine content of the adrenal glands (GOODALL & LONG 1959) as well as increased urinary excretion of these amines (BRAUN & KUSCHKE 1961, FRANZEN et coll. 1963) may occur in several animal species after whole body roentgen irradiation. A post irradiation rise in the urinary catechol amines has also been demonstrated in man (MCGOODALL 1968). Moreover, an enhanced liberation of catecholamines was observed when uterine horns of the rat were irradiated in vitro (VENINGA & BRINKMAN 1962).

With due regard to a previous finding of an increased release of catecholamines from isolated irradiated adrenal chromaffin granules (DEANOVIC & VENINGA) it seemed worthwhile to study the release pattern of catecholamines from the isolated perfused adrenal glands under the influence of roentgen irradiation.

BRINKMAN and his associates (BRINKMAN 1962, LAMBERTS & DIJKEN 1961, VENINGA 1965, BRINKMAN et coll. 1965) have maintained that the post irradiation appearance and interaction of many free neurohormones and enzymes are involved in the primary irradiation effects. It was reasonable to expect in this experimental model an increased liberation of catecholamines after lower roentgen doses as compared with those applied to the chromaffin granule suspensions.

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Table

Release rate of catecholamines from isolated perfused adrenal glands expressed in µg/min — Figures represent mean values ± standard errors

	(1) —10 to 0 min before	(2) 0 to 10 min after	(3) 10 to 20 min after	Differences (2)—(1)	(3)—(1)	(3)—(2)
Irradiation 1 000 R (N=6)	7 09 ± 2 18	8 10 ± 2 55	8 69 ± 2 40	1 05 ± 0 52 ↑	1 61 ± 0 45 ↑	0 59 ± 0 [illegible]
				n s	P < 0 02	n s
Sham irradiation Control (N = 4)	12 76 ± 1 65	12 51 ± 2 35	11 38 ± 2 54	↓ —0 25 ± 0 86	↓ —1 13 ± 0 1	↓ —0 64 ± 0 5[illegible]

Materials and Methods The left, kidney shaped, bovine adrenal glands were removed and cooled in ice within 30 minutes of slaughtering the animals, quick transport to the laboratory followed

The method of retrograde perfusion through the central adrenal vein, as originally described by HECHTER et coll (1953) and adapted by DOUGLAS & RUBIN (1961), HAAG et coll (1961), and SCHUMANN & PHILIPPU (1963), was applied This simple method consists of rapid removal of the periadrenal fat and connective tissue, followed by cannulation of the large central vein A 2 to 3 mm deep incision at the opposite side of the gland insures that the perfusate will escape The gland was mounted in a plastic organ chamber and perfused with Tyrode solution of 39°C and previously saturated with carbogen gas the perfusion pressure was 55 to 60 cm water The gland was warmed up and the remaining blood rinsed out during the first three minutes of perfusion Clear drops of Tyrode solution formed at the incision were collected in a measuring cylinder containing 0 35 ml of concentrated $HClO_4$ The perfusion rate was adjusted to approximately 10 ml 5 min by altering the pressure

Two 10 ml samples were collected and the gland was irradiated with a Siemens Dermopan roentgen generator Irradiation conditions were 50 kV, 25 mA 1 mm Al filter, tube diameter 4 cm focus to gland distance 2 5 cm and dose rate 870 R min, as measured in the water filled organ chamber The perfusion was not interrupted during the irradiation

Four samples of 10 ml perfusate were collected in the course of 20 ± 2 minutes after irradiation

The pH of the samples was adjusted to 6 0 by means of a 20 % K CO_3 solution, the precipitate was removed by subsequent centrifugation The procedure of ATKINSON & WYNNE (1962) was applied for the absorption and elution

of the catecholamines The fluorimetric method of SHORE & OLIN (1958) was employed to determine both the adrenalin and noradrenalin together with a Locarte semi spectrofluorimeter (LF 1 and B390 filters on the primary side produced an excitation at 400 mμ the monochromator on the secondary side was adjus ed to 520 mμ) The standard solution contained 2 μg/ml adrenalin, the blank consisting of 0 4 N sulfuric acid The relationship between the adrenalin concentrations below 2 μg/ml and the fluorimeter readings was linear

Results and Discussion

A dose of 1 000 R was found to be the lowest one giving a measurable effect after a number of pilot experiments

The concentration of catecholamines determined in the perfusate samples be fore irradiation varied in the experimental group between 0 2 and 1 4 μg/ml with an average value of 0 6 μg/ml post irradiation values ranged from 0 3 to 2 1 μg/ml giving a mean of 0 9 μg/ml In the sham irradiated group the con centration of these amines before treatment varied between 0 5 and 1 7 μg/ml with a mean of 1 1 μg/ml and thereafter between 0 3 and 1 7 μg/ml giving a mean of 1 0 μg/ml

The data obtained were recalculated in μg/min to correct the small differences in collection time The average values of the rate of release obtained in every 10 minute period are presented in the Table It is seen that the yield of catechol amines in irradiated glands progressively increased towards the end of the 30 minute observation period In contrast the leakage of catecholamines from the sham irradiated glands steadily decreased Only the differences in the rate of catecholamine release between the third and the first collection periods were significantly different in the irradiated and sham irradiated adrenals ($P < 0\,02$ student s t test) A distinct variation in the starting values of the release rate of catecholamines was observed between the groups

A dose as high as 1 000 R to the isolated perfused adrenal gland provokes a significant increase in catecholamine liberation As compared with our previous results with isolated chromaffin granules (DEANOVIC & VENINGA) this dose is 3 to 4 times lower However in the case of whole body exposure a dose of only 400 R leads to a significant rise in the content of urine catecholamines (FRANZEN et coll 1963 GOODALL 1968) This suggests the existence of a gradually in creasing radiation responsiveness when the release takes place in isolated sub cellular elements complete organs or in the integral organism This concept of enhanced radiation response is consistent with the idea of the potentiating inter action of liberated neurohormones and enzymes (BRINKMAN 1962 BRINKMAN et coll 1965) Taking into consideration the possibility of a simultaneously radi

Table

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	(1) —10 to 0 min before	(2) 0 to 10 min after	(3) 10 to 20 min after	Differences (2)—(1)	(3)—(1)	(3)—(2)
Irradiation						
1 000 R	7.09 ± 2.18	8.10 ± 2.55	8.69 ± 2.40	1.05 ± 0.52	1.61 ± 0.45	0.59 ± 0.71
(N=6)				↑	↑	↑
				n.s.	P < 0.02	n.s.
Sham irradiation				↓	↓	↓
Control	12.76 ± 1.65	12.51 ± 2.35	11.38 ± 2.54	—0.25 ± 0.86	—1.13 ± 0.1	—0.64 ± 0.5
(N=4)						

Materials and Methods. The left, kidney shaped, bovine adrenal glands wei removed and cooled in ice within 30 minutes of slaughtering the animals, quic transport to the laboratory followed.

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Four samples of 10 ml perfusate were collected in the course of 20 ± 2 minute after irradiation.

The pH of the samples was adjusted to 6.0 by means of a 20 % K_2CO_3 solution, the precipitate was removed by subsequent centrifugation. The pro cedure of ATKINSON & WYNNE (1962) was applied for the absorption and elution

SUMMARY

Isolated bovine adrenal glands were perfused through the central adrenal vein and irradiated with 1 000 R roentgen The catecholamine content in aliquots of the perfusate after irradiation presented a gradually increasing trend in contrast to the decrease observed in sham irradiated controls A significant difference in the release rate of catecholamines existed between the two groups The findings are discussed in relation to the possible role of catecholamines in the early neuro endocrine reactions to irradiation

ZUSAMMENFASSUNG

Isolierte Rindernebenniere wurden durch die zentrale Nebennierenvene retrograd durchstromt und mit 1 000 Rontgen bestrahlt Der Brenzcatechinamingehalt in Aliquoten der Durchstromungsflussigkeit nach der Bestrahlung zeigte eine allmahlich zunehmende Tendenz im Gegensatz zu einer abnehmenden Tendenz bei den nicht bestrahlen Kontrollen Ein signifikanter Unterschied in der Freisetzungsgeschwindigkeit der Brenzcatechinamine wurde zwischen den beiden Gruppen festgestellt Die Befunde werden mit Hinsicht auf die mogliche Rolle der Brenzcatechinamine in der neuro-endokrine Bestrahlungsfruhreaktion diskutiert

RÉSUMÉ

Les auteurs ont perfusé par la veine surrénale centrale des glandes surrenales isolees de bœuf et les ont irradiées par 1 000 roentgen La concentration en catécholamines du liquide de perfusion apres irradiation tend a augmenter graduellement contrairement à la diminution observée sur les surrénales temoins soumises a une irradiation simulee Il y a une difference significative du taux d excretion de catecholamines entre les deux groupes Les auteurs examinent ces résultats et les rapprochent du role possible des catecholamines dans les reactions neuro endocriniennes précoces a l irradiation

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ation induced release of several neurohormones (LAMBERTS & DIJKEN 1961, VENINGA 1965), it seemed reasonable to expect a liberation of acetylcholine from splanchnic nerve intramedullary terminals in the experimental object as well as in the whole organism The secretion mechanism of catecholamines (DOUGLAS 1966 SMITH 1968) might consequently be set in motion

The initial release of catecholamines in both groups of glands was distinctly different, to which three factors in particular may have contributed (1) experiments with irradiated glands and control experiments were perforce not run at the same time, (2) the duration of the terminal asphyxia in the slaughtered cattle could not be controlled so that differences in the discharge of catecholamines by agonal sympathetic nerve stimulation might have occurred, (3) the time interval between slaughtering and the start of perfusion varied from 1 to 2 hours, and the duration of the gland cooling corresponded with this time interval

It is well known that the adrenal medulla is not essential to life if the organism is unexposed to stress Since adrenalectomized animals exhibit increased radiosensitivity (CRONKITE & CHAPMAN 1950 EDELMAN 1951, BETZ 1956), there is justification for considering irradiation as a stressful condition (GOODALL & LONG 1959, BACQ & ALEXANDER 1961, BRINKMAN 1962) characterized by a typical quick neuro-endocrine reaction Although the 'classical concept of an adrenalin hypothalamus pituitary adrenal cortex chain mechanism has been laid open to criticism (VOGT 1952, GUILLEMIN 1955) it seems at present very likely that free adrenalin exerts a direct influence on the reticular activating system (ROTHBALLER 1959) With due regard to the hypothesis that the autonomic nervous system of vertebrates is more easily influenced by irradiation than the central nervous system (HUG 1962), the following concept might be deduced from the results

Catecholamines are liberated by a direct radiation effect on the adrenal medulla the free adrenalin then sets in motion the complex of neuro endocrine reactions via the reticular formation In addition, if whole body irradiation is considered a distributed stimulus (HUNT & KIMELDORF 1964), it is reasonable to suppose a simultaneous central (hypothalamic) as well as a peripheral (adrenal + sympathetic) release of neurohormones leading to mutually potentiating interactions These events might be interpreted as the principal pathogenetic factors in early radiation sickness (BRINKMAN 1962) Evidence exists that these early reactions to irradiation could exert a favourable influence with regard to the survival of the organism (BACQ et coll 1960)

Acknowledgement

The authors are indebted to Professor H B Lamberts for his constant interest and valuable criticism The technical assistance of Mrs Willy Lemstra is gratefully acknowledged

FROM THE DEPARTMENT OF RADIOTHERAPEUTICS UNIVERSITY OF CAMBRIDGE AND THE RADIOTHERAPEUTIC CENTRE, ADDENBROOKE S HOSPITAL (DIRECTOR PROF J S MITCHELL) CAMBRIDGE ENGLAND

LABELLED COMPOUND RELATED TO SYNKAVIT AND ITS UPTAKE IN CERTAIN HUMAN TUMOURS STUDIED BY RADIO ISOTOPE SCANNING

by

D H MARRIAN J S MITCHELL C H BULL E A KING and K F SZAZ

One of the most interesting properties of the compound 2 methyl 1 4 naphthaquinol bis disodium phosphate) abbreviated MNDP is that it has been found to concentrate to some degree selectively in the viable malignant cells of certain tumours MITCHELL 1960, MARRIAN MARSHALL MITCHELL & SIMON REUSS 1965) MNDP has been in use in medicine since 1941 as the synthetic vitamin K substitute Synkavit (Roche Products Ltd) It has been investigated as a radiosensitizer since 1946 (MITCHELL & SIMON REUSS 1947 MARRIAN MARSHALL & MITCHELL 1961 MITCHELL & MARRIAN 1965 MITCHELL BRINKLEY & HAYBITTLE 1965 MITCHELL 1967)

An attempt has been made since 1953 to develop radioactive drugs which are absorbed or concentrated in malignant cells to a sufficient extent to be useful in the treatment or diagnosis of patients with cancer and allied diseases Most of our investigations have concerned the therapeutic possibilities of tritiated derivatives of MNDP of extremely high specific activity (MARRIAN 1957 HORWITZ GREGG MARRIAN et coll 1959 ANDREWS BULTITUDE EVANS et coll 1962 MITCHELL

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FROM THE DEPARTMENT OF RADIOTHERAPEUTICS UNIVERSITY OF CAMBRIDGE AND THE RADIOTHERAPEUTIC CENTRE ADDENBROOKE S HOSPITAL (DIRECTOR PROF J S MITCHELL) CAMBRIDGE ENGLAND

LABELLED COMPOUND RELATED TO SYNKAVIT AND ITS UPTAKE IN CERTAIN HUMAN TUMOURS STUDIED BY RADIO ISOTOPE SCANNING

by

D H Marrian J S Mitchell C H Bull E A King and K F Szaz

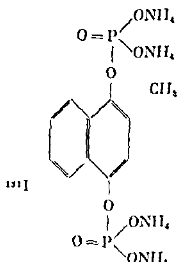
One of the most interesting properties of the compound 2 methyl 1 4 naphthaquinol bis disodium phosphate) abbreviated MNDP is that it has been found to concentrate to some degree selectively in the viable malignant cells of certain tumours Mitchell 1960 Marrian Marshall Mitchell & Simon Reuss 1963, MNDP has been in use in medicine since 1941 as the synthetic vitamin K substitute Synkavit (Roche Products Ltd) It has been investigated as a radiosensitizer since 1946 (Mitchell & Simon Reuss 1947 Marrian Marshall & Mitchell 1961 Mitchell & Marrian 1965 Mitchell Brinkley & Haybittle 1965 Mitchell 1967)

An attempt has been made since 1953 to develop radioactive drugs which are absorbed or concentrated in malignant cells to a sufficient extent to be useful in the treatment or diagnosis of patients with cancer and allied diseases Most of our investigations have concerned the therapeutic possibilities of tritiated derivatives of MNDP of extremely high specific activity (Marrian 1957 Horwitz Gregg Marrian et coll 1959 Andrews Bultitude Evans et coll 1962, Mitchell,

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KING, MARRIAN & CHIPPERFIELD 1963, CHIPPERFIELD 1967a and b, MITCHELL 1965a and b, 1966, 1967) However, it is relevant to the present investigation that MARRIAN & MAXWELL (1956) at an early stage of the work studied the distribution of radioactivity among the organs of rats bearing the Walker carcinoma 256 after intravenous injection of the labelled halogen derivatives 3-^{82}Br-bromo-2 methyl-1,4 naphthaquinol bis (disodium phosphate) and 2,3 dimethyl 5,6-di ^{131}I-iodo 1,4-benzoquinol bis (dihydrogen phosphate) Both these compounds accumulated in the tumour to a greater extent than in muscle or other tissues but the halogen atoms were quickly lost from the ring structures We were interested in 6 iodo 2 methyl 1,4 naphthaquinol bis (disodium phosphate) but at that time, it was "not possible to prepare the compound incorporating ^{131}I in sufficiently high specific activity" (MITCHELL 1956) The unlabelled compound was found to be a radiosensitizer in experiments on chick fibroblast cultures (MITCHELL, SIMON REUSS & KING 1960)

Since 1966, we have developed a method for the preparation of the labelled compound 6-^{131}I iodo 2 methyl 1,4 naphthaquinol bis (di ammonium phosphate) — abbreviated 6 ^{131}I iodo MNDP Its formula is given below



This paper is an account of the method of preparation of this compound and of the investigations carried out so far to study its uptake in certain human tumours, with special reference to its possible use in clinical radio isotope scanning

Some general considerations The immediate aim of this work was to devise a method for rapid assessment of the uptake of MNDP into malignant tumours in individual patients, in order to decide about the indications for treatment with the tritiated derivatives or with Synkavit as a radiosensitizer in conjunction with

radiotherapy However it soon became necessary to consider the relevance of these studies to the more general problem of tumour localization The quantitative results of uptake studies with tritiated MNDP (MITCHELL 1965a and b 1966 1967a CHIPPERFIELD 1967a) have shown that the initial uptake of the tritiated drugs TRA 119 and TRK 219 after intravenous injection is highest in cases of adenocarcinoma of the gastro intestinal tract although some other human tumours do not accumulate the compound

For the purpose of clinical radio-isotope scanning for studies of tumour localization ^{131}I is the most suitable halogen isotope available although its properties are not ideal (MYERS 1966) It seemed likely on chemical grounds that a halogen atom in position 6 of the MNDP structure would be less readily removed in a biologic environment than one in the 3 position although there might well be some reduction in the differential absorption ratio between tumour and normal tissue These conclusions were based on experiments with the 3 bromo-derivative of MNDP on the Walker rat carcinosarcoma 256 using fluorescence techniques (MITCHELL 1953) and labelling with ^{82}Br (MAXWELL 1954 1955 MARRIAN & MAXWELL 1956)

Recently FISHER (1968) has found that for Ehrlich ascites tumour cells incubated in 0 05 M imidazole buffer fortified with balanced salts at pH 7 4 in the absence of glucose and in the presence of air for an hour at 37 C 6 iodo MNDP at a concentration of 1 mg per ml is dephosphorylated at about the same rate and to about the same extent as MNDP at the same concentration under the experimental conditions the iodine atom remained organically bound Thus it appears that the initial step necessary for the process of absorption of the compound by the tumour cells is not influenced to an appreciable extent by the introduction of the iodine atom in the 6 position of the molecule of MNDP Further the effects of MNDP in reducing the incorporation of labelled ribonucleosides and thymidine into RNA and DNA respectively in Ehrlich ascites tumour cells in vitro are only observed fully when the pH of the medium is greater than 7 0 and when it contains glucose but they are not dependent on oxygen (HARRISON 1968)

Development of this investigation The Radiochemical Centre Amersham prepared a batch research sample of 6 ^{131}I iodo-MNDP and kindly sent us a specimen containing 0 86 mCi ^{131}I in 103 mg of compound measured on 1 July 1964 (W O No 198505) With the limited amount available we injected 86 μCi intravenously into two rats with the Walker carcinosarcoma 256 in ascitic form and then having observed no toxic effects on 4 July 1964 gave an intravenous injection of 0 32 mCi to a patient (H C No 170963) with generalized malignant melanoma

The results were suggestive but not as clear cut as we had hoped for. No further supplies of the compound were available at that time and we did not pursue the investigations. Later, we read the interesting report by GANATRA et coll. (1966) on their studies of another iodinated Synkavit labelled with ^{131}I, which "showed good concentration in spontaneous and transplanted tumors of various types in mice". Although we were not able to repeat the chemical preparation given in this paper, we were stimulated by this work to return to the investigation of 6-^{131}I-iodo-MNDP.

We prepared 18 batches of 6-^{131}I-iodo-MNDP between 27.1.1967 and 19.1.1968 inclusive; then unfortunately the work was interrupted. Each batch was first tested for toxicity on rats with the Walker carcinosarcoma 256 and then used for clinical scanning. Intravenous administration was used throughout. In all, 14 patients with advanced and inoperable tumours of various types were scanned; in 4 of these, the scanning was repeated later using another batch of compound.

Some of the earlier batches varied in their biologic activity and it became clear that the chemical purity of the preparations is of great importance.

Preparation of compound

2-Methyl-1,4-naphthaquinone-6-mercurichloride. 7.7 g of 2-methylnaphthalene-6-mercurichloride (ANDREWS et coll. 1962) was mixed with acetic acid (45 ml) and stirred. To this was added a solution of chromium trioxide (10.2 g) in water (9 ml) and acetic acid (9 ml), keeping the temperature below 50° C. The mixture was allowed to stand for 1 hour, warmed to 60° C for 30 minutes and poured into water (200 ml). The quinone was filtered off, washed with water, then methanol and dried in a warm oven. Yield 2.1 to 2.5 g of yellow solid suitable for use in the next stage without further treatment.

6-^{131}I-iodo-2-methyl-1,4-naphthaquinol bis (di-ammonium phosphate). The above quinone (0.5 g), ground finely, was suspended in absolute alcohol (15 ml) and treated with 10 mCi of ^{131}I-iodine monochloride diluted with a solution of 0.1 g iodine monochloride in dioxan (5 ml). The container was rinsed with absolute alcohol (5 ml). The mixture was stirred and refluxed for 20 minutes and a 10 % solution of iodine monochloride in absolute alcohol added (0.5 ml portions) until all the solid had dissolved. (Total reflux time is usually about 90 minutes and 2 to 3 ml of the 10 % iodine monochloride solution are needed.) While the reaction mixture was still hot, a solution of potassium iodide (5 g) in water (75 ml) was added and the whole stirred while cooling to room temperature. The precipitated quinone was allowed to settle for 10 minutes, the supernatant removed through a filter stick and the washing repeated first with more potassium iodide solution and then with water. The residual solid was stirred with a mixture of toluene (10 ml) and ethyl methyl ketone (5.5 ml) for 5 minutes and the resulting solution transferred by suction to a small separating funnel where 100 mg of 6-iodo-2-methyl-1,4-naphthoquinone m.p. 140° (ANDREWS et coll. 1962) was added with stirring. The solution was reduced by vigorous stirring with successive portions of aqueous sodium hydrosulphite. The organic layer was

washed t ice with saturated sodium chloride solution and dried by pouring through sodium sulphate The drying agent was washed with toluene The solvents were removed in vacuo the hydroquinon dissolved in redistilled pyridine (4 7 ml) and toluene (7 ml) and added slowly to a stirred solution of ice cold phosphorus oxychloride (4 7 ml) in toluene (7 ml) over 10 minutes After stirring for 1 hour the reaction mixture was allowed to reach room temperature overnight

The solvents and excess phosphorus oxychloride were distilled off in vacuo more toluene added and the evaporation repeated twice The semi olid residue was dissolved in chloro form (10 ml) and water (10 ml) and stirred during the dropwise addition of saturated lithium hydroxide solution keeping the pH at 8—10 When hydrolysis was complete (about ? hours) the solution was filtered through a pad of Hyflo transferred to a separat ing funnel and the aqueous phase washed twice with chloroform and evaporated in vacuo to about 5 ml Addition of about 10 volumes of acetone precipitated the lithium salt of the product as an oily solid which was centrifuged down dissolved in water (10 ml) acidified by the addition of concentrated hydrochloric acid (2 ml) and extracted twice with n butanol The butanol extract was added to water (50 ml) and the solution evaporated in vacuo at room temperature almost to dryness The residue was dissolved in water (4 ml) and concentrated ammonia solution (4 ml) added followed by n propanol (50 ml) The white olid was spun down and washed with solvent At this stage if tested by paper chromatography (ascending) on Whatman No 1 in n butanol (50 vol) acetic acid (20 vol) M 10 sodium acetate (30 vol) about 70 % of the radioactivity is associated with the main spot R_F=0 39) and about 30 % with slower running material

Purification of the product by paper chromato raphy The ammonium salt was dissolved in water (1 ml and loaded on large sheets of Whatman No 3MM paper pre treated with 5 % aqueous disodium ethanediamine tetra acetate and then with distilled water The paper as developed with n butanol (50 vol) acetic acid (20 vol) and water (30 vol) for 9 hours descending, dried and the areas containing pure 6-^{131}I iodo-MNDP eluted with water Thi extract was evaporated to small volume and the ammonium salt pre cipitat d as before finally giving after drying in vacuo 113 mg of ammonium salt of total radioactivity 350 μCi the specific activity was thus 3 0 mCi per mM Paper chromato-graphy showed no chemical or radiochemical impurities

Radiolo ic safety for the chemical procedures The procedures were carried out in a normal laboratory fume cupboard with an exhaust system which produced an air flow of at lea t 150 linear feet per minute across the sill at one foot opening Shielding was provided by a wall of lead bricks 2 inches thick Surgical rubber gloves were worn Film badges w r carri d on the wrist and in the laboratory coat pocket the maximum dose recorded on th s in any one month was 0 1 rad

Details of the batches p epared The yield and specific activity of the purified prepara tion of 6-^{131}I iodo MNDP varied considerably Among the 18 batches the weights of the produ t varied between 56 and 267 mg For the first 12 batches the specific activity varied between 330 and 6 0 μCi per 100 mg with mean 468 μCi per 100 mg For the last 6 batch the pecific activity varied from 540 to 1 000 μCi per 100 mg with mean 692 μCi per 100 mg corresponding to 3 11 mCi per mM calculated for the anhydrous tetra am monium salt

F r th clinical radio-isotope scanning for which intravenous injection is necessary the

single dose of the compound is preferably between 30 and 75 mg though it is likely that 100 mg would be tolerated. At least about 200 μCi is required for the scanning procedures and the single doses used so far have contained between 195 and 490 μCi.

The preparations of 6-^{131}I iodo MNDP were dissolved in pyrogen free sterile water, and the pH adjusted to 7.2 to 7.5 by adding sodium bicarbonate using the minimum amount of phenol red as indicator. The solutions were sterilised by filtration and so far have been stored in 10 ml rubber capped bottles at 3° C. Each batch was dissolved in 3 ml of solution and not more than 1.5 ml used for a single intravenous injection into a patient. Samples have been tested for sterility. Part of every batch has been used for testing by intravenous injection in relatively large doses in at least two rats with transplanted tumours primarily to exclude acute toxicity but also to examine the distribution of the compound. In these experiments, the dose of chemical injected calculated on the basis of body weight was between about 25 and 100 times that used clinically. No toxic effects were ever observed in agreement with the results of the separate experiments with rats to study the toxicity of unlabelled compound.

For reasons of radiochemical safety we have only been able to prepare sufficient 6-^{131}I iodo MNDP in each batch for use in the scanning of one patient after the necessary tests on rats.

Details of the physical measurements

Measurement of the activity of the preparations of 6-^{131}I iodo MNDP. The activity of the 6-^{131}I iodo-MNDP solutions was measured in a General Radiological Ionization Chamber of type NE 014. The chamber was calibrated with a reference solution of ^{131}I, supplied by the Radiochemical Centre, Amersham. Corrections for day-to-day changes of sensitivity were made by measurement of a radium standard.

2. *Measurement of the activity of biological specimens.* The activity of specimens of blood, urine and tissue was determined with a well type scintillation counter of type 6006 and scaler 6000 (Nuclear Enterprises Ltd, Beenham, Reading, Berkshire, England).

3. *Radio isotope scanning. Profile scanning* to obtain information about the distribution of the activity in the whole body was carried out in a number of patients using a shielded G26 lead cathode Geiger tube. The collimator was 2 cm wide, giving a 50 % resolution of about 8 cm.

Scintiscanning was carried out using a Picker Magna Scanner III with a 3×2 inch crystal. The pulse height analyser was set to accept pulses in the 320—400 keV energy range.

For scanning patients, a 19 hole lead collimator was used having a focal length of 5 cm and a 50 % resolution of 1.8 cm for a point source of ^{131}I in water. The scanning speed, line separation and time constant were chosen according to the count rate. Simultaneously two records were produced, one a photo-record on

roentgen film and the other either a colour scan or a dot (Teledeltos) record In the case of repeated scans on the same patient, the controls were reset and the background cut off level adjusted to give the best conditions for each scan The bony and other anatomical landmarks were recorded immediately before starting each scan It is essential for the patient to lie still in a comfortable position usually supine In most cases the time required for scanning was between 40 and 60 minutes The urinary bladder was emptied immediately before scanning began

For scanning rats and mice similar procedures were followed using a 31 hole collimator of a focal length of 6 cm and a 50 % resolution of 0 6 cm In most of the experiments the distribution of the activity was checked by moving the animal under the stationary collimator

Animal experiments In addition to the observations necessary to exclude acute toxicity for each batch of 6 ^{131}I iodo MNDP after intravenous injection the distribution of the activity was studied in the same animals by scanning procedures In some experiments the animal was anaesthetized with nembutal and in others it had been killed in some cases the organs were dissected out In all these examinations included 48 Wistar rats with the Walker carcinosarcoma 256 (R C H and Walpole strains) growing after transplantation subcutaneously beneath the skin of the flank 7 August rats with a transplanted hepatoma which had been induced by butter yellow and 5 mice with various spontaneous tumours

Only the first batch of the compound prepared on 27 1 1965 appeared to show selective concentration in animal tumours Seemingly positive results were found in two adult male Wistar rats with the Walker carcinosarcoma 256 (R C H strain) deeply anaesthetized with nembutal 24 mg i p followed by i p injection of 2 5 mg of potassium perchlorate in 2 5 ml saline solution and then after 30 minutes by intravenous injection of 67 μCi of 6 ^{131}I iodo-MNDP in 10 3 mg of compound dissolved in 0 5 ml of normal saline solution With the same preparation and under comparable experimental conditions there also appeared to be selective uptake in the tumour in one of two mice with spontaneous mammary carcinoma In all the other animal experiments negative results have been obtained The experimental conditions were varied After the first three experiments involving 8 rats and 2 mice nembutal anaesthesia was not used In 18 rats perchlorate in various doses was used and compared with controls without perchlorate Two rats were examined after fasting for 24 hours three were given glucose i p and nine received insulin i p None of these procedures influenced the distribution of the 6 ^{131}I iodo-MNDP The highest concentration of radioactivity was found almost invariably in the contents of the upper part of the small intestine apparently as a result of excretion in the bile, this localization was con

single dose of the compound is preferably between 30 and 75 mg though it is likely that 100 mg would be tolerated. At least about 200 μCi is required for the scanning procedures and the single doses used so far have contained between 195 and 490 μCi.

The preparations of 6-^{131}I-iodo-MNDP were dissolved in pyrogen-free sterile water and the pH adjusted to 7.2 to 7.5 by adding sodium bicarbonate using the minimum amount of phenol red as indicator. The solutions were sterilised by filtration and so far have been stored in 10 ml rubber-capped bottles at 3° C. Each batch was dissolved in 3 ml of solution and not more than 1.5 ml used for a single intravenous injection into a patient. Samples have been tested for sterility. Part of every batch has been used for testing by intravenous injection in relatively large doses in at least two rats with transplanted tumours primarily to exclude acute toxicity but also to examine the distribution of the compound. In these experiments the dose of chemical injected calculated on the basis of body weight was between about 25 and 100 times that used clinically. No toxic effects were ever observed in agreement with the results of the separate experiments with rats to study the toxicity of unlabelled compound.

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Table *(cont.)*

Histology	μCi injected	Compound mg	Comments	Assessment of scan
Acinar cubical celled carcinoma (stomach) disorderly slightly pleomorphic mucin producing carcinoma (metastasis in anterior abdominal wall)	204	31	200 mg KClO 60 minutes before injection	+ Fig 3
Only moderately well differentiated cubical and polygonal cell partly mucus secreting carcinoma (stomach p.m.)	195	46		+ Fig 1
	296	53	17 days later	+
Reticulum cell sarcoma	300	56		?
Adenocarcinoma grade I—III Dukes type B *(ascending colon)* mucin producing adenocarcinoma (metastasis in anterior abdominal wall)	253	58		—
Well differentiated adenocarcinoma	200	70		+ Fig 4
	370	70	18 days later fasting	+
Disorderly polygonal cell carcinoma (colon)	370	70		+ Fig 5
Well-differentiated adenocarcinoma with involvement of lymph nodes	300	74	Fasting	+ Fig 6
Moderately well differentiated adenocarcinoma (primary carcinoma and metastasis on bladder)	350	59	Fasting	+ Fig 7

Table

Patients investigated by scintiscanning with 6-^{131}I-iodo-MADP

Case	Sex Age (years)	Diagnosis	Previous treatment
1	F 77	Recurrent carcinoma of stomach metastases in liver and anterior abdominal wall	Partial gastrectomy 7 years previously palliative ^{60}Co γ-ray therapy with i.v. Synkavit as radiosensitizer finishing 10 weeks previously
2	F 63	Advanced carcinoma of stomach metastases in liver regional lymph nodes and peritoneum	None apart from treatment of anaemia
4	F 69	Reticulum cell sarcoma of stomach with lymph node involvement	Laparotomy gastro-enterostomy and biopsy
5	M 39	Recurrent carcinoma of ascending colon	Right hemicolectomy one year previously laparotomy and biopsy 4 weeks previously
6	M 67	Inoperable carcinoma of sigmoid colon two adjacent primaries hepatic metastases	Palliative sigmoid colectomy two weeks previously
7	F 53	Recurrent carcinoma of colon metastases in liver and anterior abdominal wall massive intra-abdominal recurrence	Transverse colectomy one year previously palliative ^{60}Co γ-ray therapy finishing 7 weeks previously
8	M 50	Carcinoma of sigmoid colon metastases in liver	Resection and end-to-end anastomosis hepatic metastases 19 months previously
9	M 55	Recurrent carcinoma of sigmoid colon metastases in liver and wall of bladder	Resection and colostomy 14 months previously laparotomy division of adhesions and biopsy 2 weeks previously

Table *(cont)*

Histology	μCi injected	Compound mg	Comments	Assessment of scan
Acinar cubical celled carcinoma (stomach) disorderly slightly pleomorphic mucin producing carcinoma (metastasis in anterior abdominal wall)	204	31	200 mg KClO 60 minutes before injection	+ Fig 3
Only moderately well-differentiated cubical and polygonal cell partly mucus-secreting carcinoma (stomach p m)	195 296	46 53	 17 days later	+ Fig 1 +
Reticulum cell sarcoma	300	56		
Adenocarcinoma grade I—III Dukes type B (ascending colon) mucin producing adenocarcinoma (metastasis in anterior abdominal wall)	253	58		—
Well differentiated adenocarcinoma	200 370	70 70	 18 days later fasting	+ Fig 4 +
Disorderly polygonal cell carcinoma (colon)	370	70		+ Fig 5
Well differentiated adenocarcinoma with involvement of lymph nodes	300	74	Fasting	+ Fig 6
Moderately well differentiated adenocarcinoma (primary carcinoma and metastasis on bladder)	350	59	Fasting	+ Fig 7

Table

Patients investigated by scintiscanning with 6-^{131}I-iodo-MNDP

Case	Sex Age (years)	Diagnosis	Previous treatment
1	F 77	Recurrent carcinoma of stomach metastases in liver and anterior abdominal wall	Partial gastrectomy 7 years previou palliative ^{60}Co γ-ray therapy with i.v. Synkavit as radiosensitizer finishing 10 weeks previously
12	F 63	Advanced carcinoma of stomach metastases in liver regional lymph nodes and peritoneum	None apart from treatment of ana
4	F 69	Reticulum cell sarcoma of stomach with lymph node involvement	Laparotomy gastro enterostomy ar biopsy
5	M 39	Recurrent carcinoma of ascending colon	Right hemicolectomy one year prev laparotomy and biopsy 4 weeks pre viously
6	M 67	Inoperable carcinoma of sigmoid colon two adjacent primaries hepatic metastases	Palliative sigmoid colectomy two weeks previously
7	F 53	Recurrent carcinoma of colon metastases in liver and anterior abdominal wall massive intra abdominal recurrence	Transverse colectomy one year pre viously palliative ^{60}Co γ-ray therap finishing 7 weeks previously
8	M 50	Carcinoma of sigmoid colon metastases in liver	Resection and end to end anastomo hepatic metastases 19 months previ
9	M [illegible]5	Recurrent carcinoma of sigmoid colon metastases in liver and wall of bladder	Resection and colostomy 14 months previously laparotomy division of adhesions and biopsy 2 weeks previou

Table (cont.)

Histology	μCi injected	Compound mg	Comments	Assessment of scan
Well differentiated mucus secreting adenocarcinoma (primary carcinoma and metastasis in scapula)	360	63	Fasting (scan of scapular regions and upper chest)	—
Well differentiated columnar cell adenocarcinoma (primary carcinoma and recurrence in sacrum)	425	50		—
More in favour of pseudomyxoma peritonei than metastatic carcinoma	345	62	Fasting	—
Unsatisfactory (drill biopsy)	303	43	Fasting	—
Unsatisfactory biopsies	230	52	200 mg $KClO_4$ orally 60 min before injection, scans at 37 min and 49 hrs after injection	—
Tubular adenocarcinoma, on the whole well differentiated and with fibrous tissue and lymphocytic reactions	280	37	Pre-operative	+ Fig 8a
	400	47	3 weeks post operative	? Fig 8b

between the tumour and adjacent soft tissues after intravenous injection of 15, 30 or even 45 mg of the compound.

The animal experiments summarized here provide no evidence for selective concentration of 6-^{131}I iodo-MNDP in the tumour studied. It is probably wise to ignore the apparently positive findings in the experiments using the first batch of labelled compound, although the possibility of unusually favourable physiological conditions involving the circulation cannot be excluded.

The negative results of the experiments as a whole is of great interest and

Table *(cont)*

Case	Sex Age (years)	Diagnosis	Previous treatment
11	F 72	Carcinoma of ascending colon recurrent metastasis in left scapula and pulmonary metastases	Excision of metastasis of left scapula 11 months previously and right hemicolectomy 10 months previously
3	M	Carcinoma of rectum local recurrence involving sacrum	Abdominoperineal resection 4 years previously
10	M 50	Pseudomyxoma peritonei	Laparotomy two months earlier appendix embedded in fixed mass in right iliac fossa extensive deposits over whole parietal peritoneum and infiltration of greater omentum course of injections of 5 fluorouracil
13	F 42	Carcinoma of right breast multiple metastases in bones	Durabolin injections
2	F 75	Carcinoma of buccal mucous membrane of cheek	Radiotherapy with 14 MeV electron beam and i v Synkavit as radiosensitizer starting *3 days previously*
14	F 61	Carcinoma of kidney	Right nephrectomy incomplete removal gross macroscopic involvement of renal vein and inferior vena cava and extracapsular spread operation specimen $21 \times 14 \times 10$ cm

firmed by autoradiography of tissue sections Other animal experiments included controls with ^{131}I in the form of sodium iodide and studies of the inhibition of uptake of ^{131}I iodide into the stomach by potassium perchlorate (see CLODE et coll 1964, GANATRA et coll 1966) Under the experimental conditions, it appears that iodide is not liberated from 6 ^{131}I iodo MNDP Further experiments were carried out in rats with the Walker carcinosarcoma 256 with the unlabelled compound 6 iodo MNDP No toxic effects were observed after intravenous injection of 30 mg in 250 g rats and roentgen examination showed no contrast

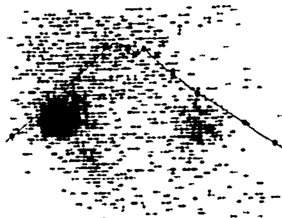


Fig 1 Case 17 Scan with 6- I iodo-MNDP

localization and detection of tumours presents many problems both physical and biologic see e g Medical Radioisotope Scanning Proc of IAEA (1964) and HOFFMANN & SCHEER (1967) However for the present purpose the methods of interpretation of the scans involve both qualitative and semi quantitative data together with a great deal of supplementary information and to a large extent are comparable with the methods used by an experienced radiologist in examining roentgen films See also SPENCER (1965)

Accordingly the results of the scanning records (see the table) have been classified as either positive (+) doubtful (?) or negative (—) These terms are defined as follows

1 Positive (+) means that there is evidence of localized uptake corresponding to the distribution of the malignant tumour

2 Doubtful (?) in the sense that the interpretation of observed localized uptake is uncertain

3 Negative (—) means that no departure from the range of normal findings can be recognized

The information about the distribution of the neoplastic tissue was independent of the results of scanning and was derived from clinical examinations radiologic investigations and surgical operations In certain cases evidence about metastases in the liver was obtained by means of scanning using radioactive colloidal gold (^{198}Au) In a number of cases valuable supplementary evidence was obtained retrospectively at post mortem examination

At the present stage of the investigation the assessment of findings within normal limits presents problems However the evidence obtained in the extensive

could offer a possible explanation for the negative results found in a number of animal experiments to study radiosensitization by Synkavit (DITTRICH & SCHIMERMUND 1953, BANE et coll 1957, COHEN & COHEN 1959, KOCH 1967) In our animal experiments, completely negative results were found with batches of 6 ^{131}I iodo MNDP which showed selective uptake into certain human tumours Supplementary investigations with the tritiated preparations of MNDP of high specific activity, TRK 219, by means of autoradiography and measurements of specific activity, have confirmed both (1) absence of selective uptake of TRK 219 into the animal tumours studied and (2) a high selective uptake of MNDP into the primary carcinoma and metastases in the liver in autopsy specimens from a patient with advanced carcinoma of the stomach (Case 12) where clinical scanning had shown selective uptake of 6 ^{131}I iodo MNDP

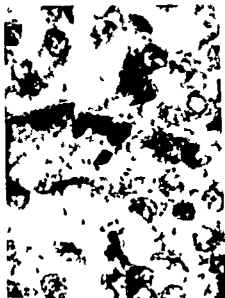
Consideration must be given to the possibility that the differences in the uptake of both MNDP and 6 ^{131}I iodo MNDP may be due to important biochemical differences between different malignant tumours not only in rats and mice but also in man (cf MITCHELL & MARRIAN 1965) It has been shown that large differences exist in enzyme activities, especially of glycerol 3 phosphate dehydrogenase (E C 1 1 1 8) even among different strains of the Ehrlich ascites carcinoma of the mouse, particularly where there are differences in growth rate (LETNANSKY 1968)

Clinical investigations

These clinical investigations sought evidence about the uptake and distribution of MNDP in advanced malignant tumours primarily to decide whether treatment of the individual patient by means of the tritiated derivative, TRK 219 was indicated However in one patient, case 2, a woman of 75, with a rather extensive carcinoma of the buccal mucosa of the cheek, the problem concerned the use of synkavit as a radiosensitizer in radiotherapy (cf KRISHNAMURTHI, SHANTA & KRISHNAN NAIR 1967) Except in this case, conventional methods of surgery and radiotherapy were unlikely to be of any value

Information about the 14 patients investigated by means of scintiscanning with 6 ^{131}I iodo MNDP is summarized in a Table The case numbers indicate the sequence of the first scan on the particular patient The arrangement of the cases in the table emphasizes the interest in malignant disease of the gastro intestinal tract Case 10 was referred with the diagnosis of adenocarcinoma but the histology and subsequent clinical course were in favour of the diagnosis of pseudomyxoma peritonei In Cases 12 and 14, the scanning provided contributory evidence of diagnostic value

The scanning procedures followed standard practice Analysis of scans for the



a



b



c

Fig. 2. Case 12. Autoradiographs of sections of autopsy specimens showing distribution of tritiated MNDP (TRK. 219). Susa fixation; staining with Ehrlich's haematoxylin. Ilford G5 liquid emulsion. For details of technique see MITCHELL, KING, MARRIAN & CHIPPERFIELD (1963). × 1 920. a) Primary carcinoma of stomach, 28 day exposure. b) Secondary carcinoma in liver, 32 day exposure. c) Normal liver, 28 day exposure.

investigations of the therapeutic possibilities of the tritiated derivatives of MNDP, already referred to, provides useful support for the recognition of normal patterns, as well as preliminary information for guidance about the kinetics of transport, uptake, distribution and excretion of the radio-iodine labelled compound. The time of beginning the first, and usually most informative, scan was in general about 30 minutes after the intravenous injection of the 6-^{131}I-iodo-MNDP. An impression has been gained that preparation of the patient by fasting, usually overnight, was advantageous. Pre-medication with potassium perchlorate is probably not necessary for scanning the stomach since there appears to be no liberation of iodide from 6-^{131}I-iodo-MNDP under the conditions of these clinical investigations. Further, in some cases, it was confirmed that no activity appeared in the thyroid.

Within the limitations of the method, the conclusions reached about the results of scanning are summarized in the table in the right-hand column. These require detailed consideration.

The patient who was investigated most fully in this series (Case 12) gave a 3-month history of weakness, anorexia and loss of weight and had severe anaemia of iron-deficiency type with haemoglobin 5·4 g per 100 ml. She was referred for scanning after a barium meal examination at which the appearance was "very suggestive of an extensive carcinoma of the wall of the stomach" in the region of the corpus and antrum. The first scan, which started at 21 minutes after intravenous injection of 195 μCi of 6-^{131}I-iodo-MNDP is shown in Fig. 1. The dimensions are given by the relation that ten lines of this photoscan corresponded to 3·2 cm. The appearances of the scan indicating some degree of selective uptake can be correlated with the distribution of the carcinoma in the stomach and in metastases in the regional lymph nodes and liver. (The autopsy findings are given below.) The general enlargement of the liver and the presence of metastases in the liver were confirmed by scanning with radioactive colloidal gold (^{198}Au). Examination with the gastro-camera showed changes strongly indicating carcinoma. It was decided that the disease was inoperable and that an attempt should be made to treat the patient with a course of intravenous injections of the tritiated drug TRK 219. During the night after the initial injection of 1·1 Ci of TRK 219 (in 12 mg of compound) the patient vomited masses of necrotic tumour. After some clinical improvement, a further scan was carried out starting at 24 minutes after intravenous injection of 296 μCi of 6-^{131}I-iodo-MNDP: the results of this scan were substantially the same as those shown in Fig. 1. A further intravenous injection of 0·50 Ci of TRK 219 (in 3·8 mg of compound) 21 days after the first injection was given. Unexpectedly three days later the patient became very ill and died with a massive pulmonary embolism.

independent of the mitotic cycle to a first approximation The evidence obtained with 6 ^{131}I iodo-MNDP by means of scanning and from tritiated MNDP by measurements of the specific activity of specimens of tumour and tissues and by means of autoradiography of histologic sections is complementary It appears reasonable to conclude that in Case 12 6 ^{131}I iodo-MNDP was taken up into the primary carcinoma and into the metastases with a distribution corresponding at least approximately to the known distribution of the neoplasm

Further information was obtained by repeating the scans at different times after the intravenous injection of 6 ^{131}I iodo-MNDP In Case 12, the first scan shown in Fig 1 was followed by further scans starting at 4 hours 28 minutes and 22 hours respectively after the intravenous injection After 4 1/2 hours much of the activity was lost from the areas of the stomach and liver but some was retained in the area below the right costal margin which corresponded to the mass of econdary glands found at autopsy in the porta hepatis and probably also to the gall bladder and considerable activity was present in the caecum and lower as ending colon By measurement of the density of the dots in the Tel edeltos scan over a square of edges 3 2 cm in the region of the stomach the apparent half life of the activity was about 2 4 hours however the errors are so great that this value can only be regarded as a crude estimate

After 22 hours the activity had disappeared almost completely from the region of the stomach and liver but was present to some extent in the area below the right costal margin and also in the ascending colon It is considered unlikely that appreciable activity could accumulate in the gall bladder in the first hour after the injection i e during the initial scan It is of interest to note that in Case 10 there was no trace of activity in the region of the gall bladder or in the palpable tumour masses of the pseudomyxoma peritonei in the initial scan tarting at 32 minutes after intravenous injection of 345 μCi though there was some activity in the urinary bladder and also in a poorly localized area in the liver above the right costal margin in a position which corresponded approxi mately to the maximum antero-posterior dimension of the liver In the subsequent scan which started at 27 1/4 hours after the injection the activity appeared to correspond to the ascending colon and splenic flexure of the colon

In the second series of scans in Case 12 the initial scan starting at 24 minutes after the intravenous injection of 296 μCi was very similar in pattern to Fig 1 The second scan at 19 hours after the injection showed no activity over the stomach and liver but a little activity in the area below the right costal margin and in the ascending colon In the subsequent scan at 66 1/2 hours after the injection activity was present to some extent in the area below the right costal margin and also in the transverse and descending colon

From these studies of scanning at different times after intravenous injection

The details of the distribution of the carcinoma were confirmed by the findings at the autopsy by Dr M J Mitchison On the postero superior wall of the stomach is a large circular ulcer (10×6 cm) with heaped up rolled edges and irregular floor Other firm nodules with grey white cut surface (up to 3 cm diameter) some umbilicated are seen in the submucosa of the stomach nearby The mass in the stomach is closely adherent superiorly to the left lobe of the liver, and on the cut surface grey white firm tissue extends directly through from the stomach mass into the liver Numerous nodules mainly umbilicated (up to 5 cm diameter) are scattered throughout the liver The pancreas is closely surrounded by numerous grey white nodules resembling secondary deposits in lymph nodes The peritoneum is studded diffusely with nodules up to approx 2 cm diameter The omentum contains a few similar deposits Lymph nodes in the para aortic porta hepatis pancreatic, iliac and tracheobronchial groups are enlarged

Additional evidence about the distribution of MNDP has been obtained on autopsy specimens by measurement of the specific activity of tritium and by autoradiography on histologic sections The techniques used have been described by MITCHELL KING, MARRIAN & CHIPPERFIELD (1963)

The measured values of the specific activity of the tissue specimens in samples of weight 10 to 40 mg were as follows

Primary carcinoma of the stomach	11 3 (± 5 %) μCi per g
Secondary carcinoma in liver, partly necrotic and containing normal tissue	5 9 (± 6 %) μCi per g
Normal liver	3 7 (± 2 %) μCi per g

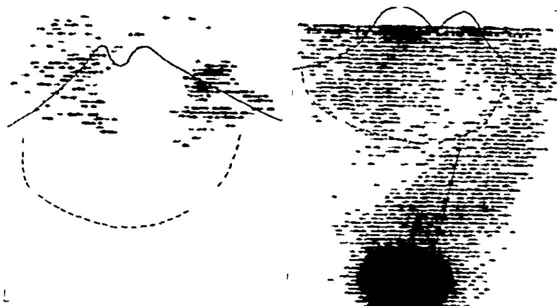
Typical autoradiograms of the primary carcinoma, secondary carcinoma in the liver and normal, though somewhat autolysed, liver tissue are shown in Fig 2 It is clear that the concentration of TRK 219 is considerably higher in the cells of the proliferating areas of both the primary and metastatic carcinoma than in normal liver In general, the measured values of the specific activities of macroscopic specimens underestimate the degree of concentration in viable tumour cells because of the presence of normal cells in various proportions and of degenerating tumour cells The body weight was 55 5 kg so that for an assumed uniform distribution of the TRK 219, the specific activity would be 9 0 μCi per g initially and would fall to 4 5 μCi per g after one biologic half life The value of this is uncertain but it is probably less than 3 days The first injection can be neglected Thus the specific activity of the normal liver observed after the injection of 0 50 Ci is not inconsistent with a value associated with uniform distribution in the normal tissues The ratio of the mean specific activities of the viable tumour cells and of normal liver tissue is at least about 3 for MNDP at 3 days after a single intravenous injection The detailed distribution of the uptake among the proliferating tumour cells is not known but it appears to be

In a patient with a very advanced reticulum cell sarcoma of the stomach (Case 4) there was no uptake into the greater part of a huge mass of tumour about 18 cm in diameter in the upper abdomen but there was a very considerable uptake over an irregular crescentic region about 13 cm long and 4 cm at its widest at the right edge of the palpable tumour This region of uptake could correspond with the previous operation finding of "enormous glands in the lesser omentum and greater omentum in addition to "a huge tumour complex arising probably from the pyloric end of the stomach However, it is not clear why the uptake was limited to such a localized area and the interpretation of this must be regarded as uncertain

Turning to the six cases of advanced carcinoma of the colon scanning gave results which have been regarded as negative in Cases 5 and 11 In both of these the histologic report included a reference to the production of mucus by the adenocarcinoma It has already been noted that the result of scanning was negative in Case 10 in which the diagnosis was regarded as pseudomyxoma peritonei In the other four cases of advanced carcinoma of the colon all with known metastases in the liver (Cases 6 7 8 and 9) positive results were obtained in the initial scans

In Case 6 the most important scan is shown in Fig 4 This scan began 40 minutes after intravenous injection of 200 μCi in 70 mg of compound At the operation it was found that the liver was huge with typical umbilicated malignant deposits most of the residual tumour consisted of secondary nodes in the left side of the abdomen and there were other nodes extending across the abdomen lower down in the mesentery of the sigmoid colon Accordingly the distribution of uptake of activity corresponded closely to the macroscopic distribution of the tumour noting of course the accumulation in the urinary bladder An essentially comparable distribution though with apparently less uptake in most areas of the tumour was observed at the subsequent scan after treatment by means of a course of intravenous injections of TRK 219

In Case 7 the localized uptake shown in the initial scan (Fig 5) corresponded to the recently developed massive abdominal recurrence whereas the liver and a lower abdominal mass which had received previous radiotherapy showed little or no uptake In Case 8 there was a huge liver with palpable metastases found at operation 19 months previously The initial scan (Fig 6) began at 42 minutes after intravenous injection of 300 μCi in 74 mg of compound and took 60 minutes to complete The liver showed uptake attributable to mestastases though it is possible that the area of very high uptake was due to accumulation in the gall bladder The uptake below the edge of the liver to the left of the umbilicus was probably due to secondary lymph nodes In Case 9 the liver was huge and contained numerous metastases The initial scan (Fig 7) began 32 minutes after



Figs 3 and 4 Cases 1 and 6 Scans with 6-^{131}I iodo-MNDP

of 6-^{131}I iodo-MNDP, it is clear that the initial uptake into the neoplastic tissue both primary and metastatic, decreases rapidly with a half life of a few hours While the main excretion from the body as a whole is in the urine with accumulation of the activity in the urinary bladder the distribution pattern changes apparently as a result of excretion in the bile with subsequent accumulation of some activity in the gall bladder and later concentration of activity in the colon From the point of view of tumour localization the best time for scanning is probably between about 30 and 60 minutes after the intravenous injection

The scan for the other patient in this series with an advanced carcinoma of the stomach (Case 1) is shown in Fig 3 This scan began at 38 minutes after the intravenous injection of 204 μCi in 31 mg of compound and required 66 minutes which was undesirably long Histologic evidence of recurrence was obtained from a mass in the anterior abdominal wall continuous with the residual epigastric mass outlined on the scan Barium meal examination showed no lesion in the gastric loculus remaining after the Billroth I partial gastrectomy The uptake of activity appeared to correspond to extensive recurrent carcinoma around the region of the stomach in parts of the mass in the anterior abdominal wall and epigastrium, in lymph nodes in the porta hepatis and in widespread metastases in the liver

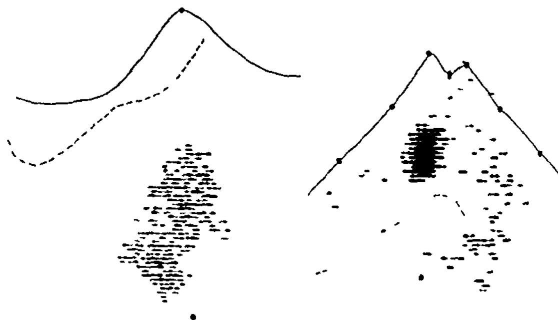
The main part of the epigastric mass which had regressed after radiotherapy showed very little uptake

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Figs 5 and 6 Cases 7 and 8 Scans with 6 ^{131}I iodo MNDP

intravenous injection of 350 μCi in 59 mg and took 40 minutes The distribution of the activity corresponded with the enormous liver containing widespread metastases, there was probably evidence of secondary lymph nodes in the left side of the abdomen below and separate from the liver There was no evidence of accumulation of activity in the gall bladder in this scan, i e within 72 minutes after the injection but there appeared to be accumulation in the gall bladder after 19 hours

Negative results were obtained with scanning in single cases of recurrent carcinoma of the rectum (Case 3), carcinoma of the breast (Case 13) and carcinoma of the buccal mucous membrane of the cheek (Case 2) However, further studies are necessary in all these diseases

The last patient in the table (Case 14) is of great interest, though presenting some problems The patient, a woman of 61 gave a history of anorexia and loss of weight for three months and was found to have a very large carcinoma of the right kidney Histologic examination of the operation specimen showed that the tumour was a tubular adenocarcinoma The report on selective arteriography by Dr D McC Gregg was as follows A huge malignant tumour is demonstrated occupying the upper and middle part of the right kidney There is diffuse pathological circulation and areas in this tumour suggesting that there is much necrosis [illegible] uperior capsular arteries are displaced upwards and

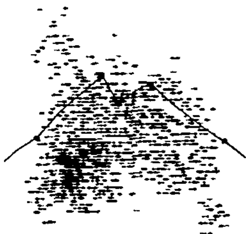


Fig 7 Case 9 Scan with 6 Iodo-MNDP

around the tumour and it is possible that there is much capsular involvement It is possible that there is venous involvement also as only a rather small vein is seen to fill with contrast medium draining the lower pole region of this kidney — At operation these findings were completely confirmed The liver was pushed up by the very large tumour and the duodenum was pushed over but not invaded A nephrectomy was carried out but there was extra capsular spread and the surgical removal was regarded as incomplete There was gross macroscopic involvement of the renal vein and a mass of growth was extracted from the inferior vena cava

The pre operative scan shown in Fig 8a began 32 minutes after intravenous injection of 280 μCi and took about 38 minutes ten lines of the scan corresponded to 3 2 cm The distribution of uptake corresponded in general to the position of the huge renal tumour crossing the midline in its upper part between the xiphoid and the top of the scan The necrotic avascular area shown in the arteriogram appears to correspond to the region of low uptake to the right of the upper part of the costal margin The lower pole of the right kidney below the tumour mass was relatively normal in structure and no uptake was seen The area of high uptake above and to the right of the umbilicus probably corresponded to growth in the right renal vein and inferior vena cava However, the region of moderately high uptake above and below the left costal margin has not been explained It disappeared along with the main mass of the tumour after the

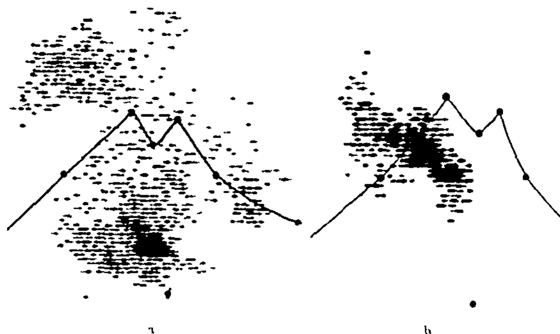


Fig 8 Case 14 Scans with 6 ^{131}I iodo MNDP a) Pre operative scan b) Scan 3 weeks after operation

operation The scan at 3 weeks after operation is shown in Fig 8b It i to be noted that for this scan a substantially larger activity, 490 µCi was used It was assumed that the area of high uptake running across the right costal margin indicated residual growth in the tumour bed but it must be emphasized that there is some uncertainty in this interpretation

Discussion and Conclusion

The evidence shows that in some advanced human malignant diseases the uptake of 6 ^{131}I iodo MNDP demonstrable by scanning, corresponds to a large extent to the known macroscopic distribution of the primary and metastatic tumours For the purpose of tumour localization, the best time for scanning is probably between about 30 and 60 minutes after the intravenous injection, in these studies, the activity injected has varied between 194 and 490 µCi and mainly between 200 and 400 µCi, in 31 to 74 mg of compound These activities are regarded as acceptable in the investigation of the individual patients under consideration in a t ing 330 µCi, the total dose of radiation delivered to the

kidney is not likely to exceed about 1 5 rad and the dose to other normal tissues is considerably less The length of time required for scanning has been undesirably long The main route of excretion is in the urine with concentration in the urinary bladder From a practical point of view it is important for the bladder to be emptied immediately before scanning The activity concentrated in the tumour decreases rapidly with a main apparent half life of a few hours It is important to scan at the rather critical time of maximum accumulation in the tumour Moreover in later scans the picture can be confused by excretion in the bile accumulation in the gall bladder and subsequent concentration in the colon

In this investigation positive results were obtained in the initial scanning of two cases of advanced carcinoma of the stomach in four out of six cases of advanced carcinoma of the colon and in one case of advanced tubular adenocarcinoma of the kidney The correspondence between the observed distribution of activity and the known distribution of viable tumour was in general close but certain discrepancies which were difficult to understand have been noted It has been shown that the evidence obtained with 6 ^{131}I iodo-MNDP and with tritiated MNDP is complementary

The negative results obtained with some human tumours and with a number of experimental tumours in rats and mice may reflect biochemical differences between different individual tumours

It is clear that much further work is required including a general survey of different types of human tumours together with a detailed study of cases of adenocarcinoma of the gastro-intestinal tract and particularly of early cases

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SUMMARY

An account is given of the method of preparation of the labelled compound 6-^{131}I iodo 2 methyl 1 4 naphthaquinol bis (di-ammonium phosphate) (abbreviated 6-^{131}I iodo-MNDP and of investigations carried out so far to study its uptake in certain advanced human malignant tumours and in some experimental tumours in rats and mice Supplementary evidence with tritiated MNDP is considered

ZUSAMMENFASSUNG

Eine ausführliche Beschreibung der Präparation einer Isotopen Verbindung 6 ¹³¹J Jodo Methyl 1,4 Naphthochinol bis (di Ammoniumphosphat) abgekurzt 6 ¹³¹J Jodo MNDP wird gegeben und es wird über Studien ihrer Aufnahme in gewissen avancierten menschlichen malignen Tumoren sowohl als in gewissen experimentellen Tumoren in Ratten und Mäusen berichtet Die Verfasser haben eine komplettierende Studie dieser Fixierung mittels des Präparates Tritium MNDP ausgeführt

RÉSUMÉ

Les auteurs décrivent une méthode de préparation du composé marqué 6 ¹³¹I iodo ? méthyl 1 4 naphthaquinol bis (di ammonium phosphate), en abrégé 6 ¹³¹I iodo MNDP, et décrivent les recherches faites pour étudier sa fixation dans certaines tumeurs malignes humaines avancées et dans certaines tumeurs expérimentales de rats et de souris Ils examinent une étude complémentaire de cette fixation au moyen du MNDP tritié

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FROM THE DEPARTMENT OF THERAPEUTIC RADIOLOGY (DIRECTOR J H WEBSTER)
ROSWELL PARK MEMORIAL INSTITUTE BUFFALO NEW YORK U S A

CHANGES IN TUMOR OXYGEN TENSION DURING RADIATION THERAPY

by

A O BADIB and J H WEBSTER

In different biological systems the sensitivity to radiation is positively correlated with the concentration of free oxygen in the system (GRAY 1957) Well oxygenated tumor cells are more sensitive to irradiation than anoxic tumor cells (GRAY et coll 1953 GRAY 1957 1961) Quantitative measurements of tissue oxygen tension have been used in the study of the influence of oxygen breathing on the tumor oxygenation (CATER & SILVER 1960 and CATER 1964) and in the assessment of the radiocurability in carcionoma of the cervix (KOLSTAD 1964) Serial determination of possible changes in tumor oxygenation during irradiation and their correlation with the clinical response has been recommended by KOLSTAD

In this study the changes in tumor oxygenation during irradiation using three different fractionation patterns were recorded and correlated with radiation response of different tumors accessible for evaluation

Materials and Methods The material investigated (Table 1) comprised sixty eight cases selected from those referred to the Radiotherapy Department of Roswell Park Memorial Institute during September 1966 and September 1967 These are cases presenting with superficial and accessible tumor masses Thirty

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Table 1

Materials

Primary	Histology	Number of cases	Site examined	Size (cm²) Mean (range)
Oropharynx*	Squamous cell carcinoma	34	Cervical lymph nodes	42 (26—54)
Breast	Scirrhous carcinoma	6	Supracl. lymph nodes	48 (24—60)
Lung	Anaplastic carcinoma	6	Supracl. lymph noeds	
Bladder	Transitional cell carcinoma	4	Inguinal lymph nodes	
Lymphoid tissue				
	Reticulum cell sarcoma	6	Cervical and axillary lymphadenopathy	75 (60—110)
	Lymphocytic lymphosarcoma	5		
	Hodgkin's disease	6		
	Giant follicular	1		

*This includes tumors of tonsillar fossa (18 cases), pharyngeal wall (12 cases) and soft palate (4 cases).

four had squamous carcinoma of the oropharynx with cervical lymph node metastases (grade I-17, grade II 11, and grade III 6). Sixteen cases of other epithelial tumors included scirrhous carcinoma of the breast (6 cases) and anaplastic carcinoma of the lung (6 cases) both with supraclavicular lymphadenopathy and transitional carcinoma of bladder (4 cases) with inguinal lymphadenopathy. Eighteen cases were lymphomas (six reticulum cell, five lymphocytic lymphosarcoma, six Hodgkin's and one giant follicular lymphoma) with cervical and axillary lymphadenopathies. All lymphomas were stage II cases.

Radiation treatment using cobalt 60 (10.4 mm Pb HVL) and 2 MeV (7.6 mm Pb HVL) units was given as follows:

1. Conventional daily fractionation: 200 rad daily tumor dose to a total of 5 000—6 000 rad given in ten cases of metastatic squamous carcinoma of the oropharynx and ten cases of metastatic carcinoma of breast (4 cases), lung (4 cases), and bladder (2 cases).

2. Split dose radiation: 250—300 rad tumor dose daily for a total of 5 000—6 000 rad in two halves with two weeks rest in between, given in 18 cases of metastatic squamous carcinoma of oropharynx and 6 cases of metastatic breast, lung and bladder carcinoma (2 cases each).

3. Weekly doses: 725 rad tumor dose once weekly for four increments, given in 6 cases of metastatic squamous carcinoma of the oropharynx.

4. In lymphomas, conventional daily fractionations of 150—200 rad tumor dose was given for a total of 3 500—4 500 rad.

Table 2

Values in mm Hg (mean ± standard error and range) of the tissue oxygen tension in cervical lymph node metastasis of the squamous cell carcinoma of oropharynx

Conventional				Split dose			Weekly dose		
Onset of treatment	No of cases	Tumor pO	Tumor bed pO	No of cases	Tumor pO	Tumor bed pO	No of cases	Tumor pO	Tumor bed pO₂
0 weeks	10	24 6±1 9 (14—34)	41 8±3 4 (18—58)	18	?4 2±1 8 (1?—39)	42 0±2 4 (18—58)	6	24 8±4 7 (8—38)	40 0±4 7 (24—60)
1	10	2? ±6? 1 (14—3?)	44 0±3 2 (22—60)	18	27 6±? 1 (1?—44)	43 7±2 2 (16—?1)	?	29 3 5 2 (14—44)	41 5±5 2 (22—?2)
?	10	?8 0±2 3 (15—3?)	45 ?±3 7 (?0—60)	18	30 0±2 2 (14—46)	4? 0±2 6 (20—63)	6	33 5±6 ? (16—49)	42 6±5 2 (25—6)
3	10	30 1±? 4 (17—42)	4? 0±3 5 (24—6?)	18	33 4±2 4 (16—46)	44 0±2 6 (18—60)	6	35 2±6 1 (18—52)	42 0±5 2 (25—64)
4	10	3? 0±2 6 (18—4?)	46 8±3 4 (28—64)	18	3? 3±2 7 (15—57)	42 0±2 5 (18—60)	6	34 3±6 2 (15—50)	44 0±4 7 (30—64)
5	10	3? 4±2 6 (16—44)	4? 1±3 5 (22—58)	18	3? 9±? 9 (14—59)	43 3±2 ? (16—60)			
6	6	30 8±3 4 (20—44)	4? 3±3 1 (38—60)	16	34 0±? 5 (16—55)	46 2±2 6 (20—65)			
1 month	4	26 3±2 4 (20—30)	44 5±3 2 (36—48)	10	?8 4±1 3 (18—36)	44 0±2 8 (20—6?)	4	?6 5+5 2 (18—42)	39 3+4 1 (28—?8)
3	4	26 3±? 5 (20—28)	4? 0±3 3 (34—43)	3	22 0±3 0 (16—2?)	43 6±2 5 (20—58)			

In carcinomas two lateral opposing fields were used for irradiation of cervical lymph node metastases and direct single field for supraclavicular and inguinal lesions In lymphomas a mantle field was used to treat the neck mediastinum and axillae in all the cases

The tissue oxygen tension was measured in the tumor center and in the normal tissues of the tumor bed included in the radiation field Measurements were made at the same sites before treatment weekly during treatments and in residual tumor masses of suitable size one and three months after the end of treatment A platinum microelectrode (made by Beckman Palo Alto California) was used with 0 0005 inch thickness sealed in glass except for the tip and cemented within a silver anode When used the tip of the electrode was covered by a thin polyethylene membrane filled with KCl solution which was changed and checked under the microscope before each measurement The electrode was connected to

Table 1

Materials

Primary	Histology	Number of cases	Site examined	Size (cm) Mean (range)
Oropharynx*	Squamous cell carcinoma	34	Cervical lymph nodes	42 (26—54)
Breast	Scirrhous carcinoma	6	Supracl lymph nodes	48 (24—60)
Lung	Anaplastic carcinoma	6	Supracl lymph noeds	
Bladder	Transitional cell carcinoma	4	Inguinal lymph nodes	
Lymphoid tissue				
	Reticulum cell sarcoma	6	Cervical and axillary lymphadenopathy	75 (60—110)
	Lymphocytic lymphosarcoma	5		
	Hodgkin s disease	6		
	Giant follicular	1		

*This includes tumors of tonsillar fossa (18 cases) pharyngeal wall (12 cases) and soft palate (4 cases)

four had squamous carcinoma of the oropharynx with cervical lymph node metastases (grade I-17, grade II 11, and grade III 6) Sixteen cases of other epithelial tumors included scirrhous carcinoma of the breast (6 cases) and anaplastic carcinoma of the lung (6 cases) both with supraclavicular lymphadenopathy and transitional carcinoma of bladder (4 cases) with inguinal lymph adenopathy Eighteen cases were lymphomas (six reticulum cell, five lymphocytic lymphosarcoma, six Hodgkin s and one giant follicular lymphoma) with cervical and axillary lymphadenopathies All lymphomas were stage II cases

Radiation treatment using cobalt 60 (10 4 mm Pb HVL) and 2 MeV (7 6 mm Pb HVL) units was given as follows

1 Conventional daily fractionation 200 rad daily tumor dose to a total of 5 000—6 000 rad given in ten cases of metastatic squamous carcinoma of the oropharynx and ten cases of metastatic carcinoma of breast (4 cases), lung (4 cases) and bladder (2 cases)

2 Split dose radiation 250—300 rad tumor dose daily for a total of 5 000—6 000 rad in two halves with two weeks rest in between given in 18 cases of metastatic squamous carcinoma of oropharynx and 6 cases of metastatic breast, lung and bladder carcinoma (2 cases each)

3 Weekly doses 725 rad tumor dose, once weekly for four increments given in 6 cases of metastatic squamous carcinoma of the oropharynx

4 In lymphomas conventional daily fractionations of 150—200 rad tumor dose was given for a total of 3 500—4 500 rad

Table 4

Values in mm Hg (mean ± standard error and range) of the tissue oxygen tension in the lymphoma group

After onset of treatment	Number of cases	Mean pO_2 (range pO_2)	
		Tumor pO_2	Tumor bed pO_2
0 weeks	18	26 4±1.8 (10—36)	40 0±2 2 (24—60)
1	18	29 9±2 0 (12—40)	4? 0±2 5 (?4—6?)
2	18	34 4±2 3 (12—46)	43 5±2 4 (?6—66)
3	18	36 3±2 4 (14—46)	44 0±2 3 (?6—6?)
4	11	32 3±2 7 (15—42)	44 3±2 2 (26—68)
1 months	6	26 2±3 1 (15—3?)	41 5±2 5 (32—5?)
3	3	17 0±1 0 (1?—18)	43 0±2 4 (32—54)

study in Tables 2, 3 and 4 The mean values of pO_2 are plotted in Figs 1 to 3 for each group of tumors during irradiation

A lower oxygen tension was observed in all the tumors in the initial (pretreatment) measurements as compared in all the tumors in the bed (Tables 2 to 4) The difference between the mean pO_2 in the tumor and that in the normal tissue was statistically significant ($p<0\ 001$) The range and mean values of initial tumor pO_2 in the carcinomas and the lymphomas were not significantly different Also the initial oxygen tension in the normal tissues of the different tumor beds was of equal means and ranges with no significant differences

Serial determination showed a progressive increase in tumor oxygenation during irradiation in all the groups (Figs 1 to 3) In tumors treated by conventional daily fractionation the percentage increase in oxygen tension at the end of irradiation was 46 % in lymphomas 32 % in squamous carcinomas and 29 % in other types of carcinomas The improvement reached its maximum at the end of irradiation The increase in oxygenation of tumors receiving split dose irradiation was 50 % in squamous carcinoma and 45 % in the other types of carcinomas Almost all the increase was established before the start of the second half of the irradiation split course and after the first two doses of weekly fractions

Table 3

Values in mm Hg (means ± standard error and range) of the tissue oxygen tension in lymph node metastases of carcinomas of breast, lung and bladder

Conventional				Split dose		
After onset of treatment	Number of cases	Tumor bed pO_2	Tumor pO_2	Number of cases	Tumor pO_2	Tumor bed pO_2
0 weeks	10	21.0±2.7 (8—35)	41.0±3.0 (20—54)	6	21.3±3.4 (10—30)	40.5±4.4 (24—56)
1	10	23.0±2.9 (8—38)	42.7±3.2 (22—60)	6	25.7±4.2 (10—36)	4[illegible].5±4.6 (24—54)
2	10	25.0±2.7 (10—35)	44.0±3.2 (22—60)	6	27.7±4.0 (14—39)	43.7±5.4 (2[illegible]—60)
3	10	26.5±2.9 (10—36)	45.2±3.3 (22—60)	6	28.8±4.6 (13—40)	43.0±5.1 (25—60)
4	10	26.9±3.0 (10—30)	44.3±3.5 (20—62)	6	29.7±4.3 (14—40)	41.6±5.[illegible] (20—60)
5	6	21.5±2.9 (10—30)	46.0±3.6 (22—64)	6	31.3±5.2 (14—45)	43.0±[illegible] (24—60)
6				3	28.0±4.5 (20—36)	43.3±5.2 (26—58)
1 months	5	17.0±2.8 (10—25)	43.6±3.5 (20—58)	0		
3	4	15.7±2.4 (10—22)	41.0±3.0 (2[illegible]—58)	0		

an amplifier providing a constant polarizing voltage (—0.6 V). The current was amplified and read on a scale calibrated against a known oxygen sample (compressed air bubbling through distilled water) and an oxygen free sample (nitrogen bubbling through distilled water) at 37° C controlled temperature. The calibration was done before and after in vivo measurements and the accuracy and response time of the electrode were also tested. The stability was greatly increased by assembling the electrode, some time before use, with the polarization voltage applied. The electrodes were sterilized in zephiran.

Patients were followed monthly after treatment for at least six months to assess the response of irradiation.

Results

The measurements of tissue oxygen tension in tumor and tumor bed during radiation are presented as mean and range values in the three groups of the

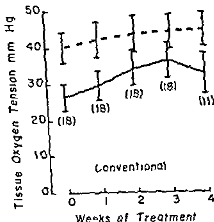


Fig 3 Variations in tissue oxygen te (mean values in tumor —— and tumo) during irradiation in malignant phomas Vertical bars represent 95 dence intervals The number of cases are in brackets

The initial (pre treatment) oxygen tension values in squamous cell carci that persisted after conventional daily fractionated irradiation were higher the initial oxygen tension values in squamous carcinomas that persisted split dose radiotherapy (Table 5) Metastatic carcinomas of the breast, lun bladder treated by split dose radiotherapy regressed within three mon irradiation while four cases of this group (one breast one lung and two bla with equal pretreatment size and oxygenation persisted after conventional radiotherapy (Table 3)

Discussion

The oxygen tension of tumor cells depends on oxygen diffusion from bl the capillaries of the stroma and this is influenced by the intercapillary di the diffusion coefficient of oxygen and the oxygen consumption of the cells (KETY 1957 and CHURCHILL DAVIDSON et coll 1957) The determ of oxygen tension in tumors was early computed from equations based or sion models (KETY 1957) and assumed histologic structure (THOMLIN GRAY 1955) Polarographic methods helped later in the quantitative m ments of tumor oxygenation in vivo (CATER & SILVER 1960)

Many difficulties exist in the determination of variations in tumor tension due primarily to the insufficiency of the present methods The ele us d are criticized for their size and poor spatial resolution (KOLSTAD The distortion of the tumor structure and of the capillary arrangement point of electrode insertion also influence the diffusion process (GRAY EVANS & NAYLER (1963) found that measurement at one site in some

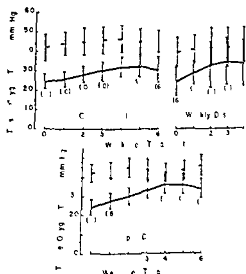


Fig. 1. Variations in tissue oxygen tension (mean values in tumor —— and tumor bed ----) during irradiation in metastatic squamous cell carcinoma of the oropharynx. Vertical bars represent 95 % confidence intervals. The number of cases are given in brackets.

The irradiated normal tissues in the tumor bed showed a similar but smaller change in oxygenation (Tables 2 to 4). No more than 10 % increase was seen during the first two weeks of conventional daily fractionation and weekly doses and during the two halves of the split dose. This increase was, however, statistically significant ($p<0.001$).

A correlation of the clinical radiation response with the initial and final tumor oxygenation is given in Table 5. This response was assessed by the degree of tumor regression within three months of the end of irradiation. The period of observation in this study will allow only the assessment of short term tumor regression and not cure rate. The initial mean value of oxygen tension in persistent lymphomas (one case of reticulum cell sarcoma, one case of lymphosarcoma and one case of Hodgkin's) was significantly lower than the initial values in the lymphomas which completely regressed ($t=10$, $p<0.001$). The same finding was seen in carcinomas treated by daily conventional and split course techniques.

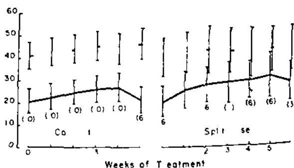


Fig. 2. Variations in tissue oxygen tension (mean values in tumor —— and tumor bed ----) during irradiation in metastatic carcinomas of the breast, lung and bladder. Vertical bars represent 95 % confidence intervals. The number of cases are given in bracket.

and EVANS & NAYLOR (1963) Earlier MOTTRAM (1936) postulated that the elimination of radiation damaged tumor cells may be followed by a better oxygenation of the tumor

In all the tumors irradiated by a conventional daily fractionated course, the lymphomas showed the highest increased rate of tumor oxygenation This may be related to an earlier tumor regression of these radiosensitive tumors allowing better circulation in a more normal vascular pattern (URBACH & NEOLL 1958) Comparing the three fractionation patterns used the greatest improvement in oxygenation was observed in tumors irradiated by split course using relatively large fractions delivered in two short periods with a rest interval between This allows more time for tumor regression and subsequently better blood supply to the hypoxic centers. In addition an increase in the relative availability of the oxygen to the hypoxic tumor cells can be achieved by properly fractionated radiation (THOMLINSON 1967) which can affect first the well oxygenated cell. In our material a plateau in tumor oxygenation was usually established at a maximum value before second half of the split course was given This is of importance in the less radiosensitive hypoxic tumors It may explain the good initial clinical response in SCANLON's series (1963) and in our own clinical trials in advanced head and neck tumors irradiated by split course

The number of cases receiving weekly doses was relatively small however the observations suggest a similar pattern to that in the split dose radiotherapy

The observed initial oxygen tension in tumors that persisted within three months of irradiation was the lowest in the whole series with ten out of fourteen tumors having an initial oxygen tension below 15 mm Hg compared to only four out of fifty four apparently regressed tumors This suggests that the critical initial oxygen tension value in these tumors is near 15 mm Hg above which good response to radiotherapy is expected

In squamous carcinomas, persistent tumors after conventional daily irradiation had a higher initial oxygen tension value than persistent tumors after split dose radiotherapy At the same time metastatic carcinomas of breast, lung and bladder regressed within three months of split dose radiotherapy while similar tumors with equal pretreatment oxygenation persisted after conventional daily irradiation These findings may indicate a greater chance of persistance in hypoxic tumors treated with conventional daily fractionation than with split dose radiation This can be related to a higher rate of early improved oxygenation in the split radiation course

A clinical study of a homogenous material irradiated by different fractionation patterns and observed for a long period of time is desirable to correlate the changes in tumor oxygenation during irradiation and the initial tumor response with the chance of cure

Table 5

Correlation between tumor oxygen tension measurements and the clinical response

	Cases with complete regression*		Cases with persistent tumor**	
	Initial pO_2	Final pO_2	Initial pO_2	Final pO_2
Metastatic squamous carcinoma of oropharynx	Conventional			
	28.3±2.4 (24—34)	37.7±2.5 (32—44)	19.0±4.5 (14—22)	26.3±2.5 (20—28)
	Split dose			
	26.3±1.5 (18—38)	42.1±2.9 (27—59)	14.0±1.2 (12—16)	22.0±3.0 (16—25)
Metastatic carcinomas of breast, lung and bladder	Conventional			
	26.7±2.3 (20—35)	33.3±3.4 (27—38)	12.5±2.1 (8—18)	15.7±2.4 (10—22)
Malignant lymphomas	Conventional			
	29.5±1.3 (14—36)	41.5±2.[illegible] (30—48)	11.3±0.7 (10—12)	17.0±1.0 (15—18)

* Tumor less than 25% of the original size at the end of irradiation and regressed completely within three months of irradiation.

** Residual tumor (more than 25% of the original size) within three months of completion of irradiation.

may not represent the oxygen tension at other sites because of lack of homogeneity of the vascular pattern in these tumors. For this and other reasons given, the values of oxygen tension determined by polarography can be considered only to represent the average tumor oxygen tension. Differences between single readings in the same case and between series of readings may be considered real (KOLSTAD 1964).

The electrode used in this study has the advantage of being less influenced by movements and of a reduced sensitivity drift (CLARK 1956, and CONNELLY 1957). The obtained calibration curves for this electrode seem to be valid for measurements in tissues (KOLSTAD 1964).

The improved tumor oxygenation during radiation therapy in all tumors suggested that partial tumor regression relieved the pressure on the capillaries and restored the normal blood flow with better oxygen diffusion to the hypoxic parts of the tumors. A similar finding was reported by CATER & SILVER (1960).

GRAY L. Oxygenation in radiotherapy I Radiobiological consideration Brit J Radiol 30 (1957) 403
— Radiological basis of oxygen as a modifying factor in radiation therapy Amer J Roentgenol 85 (1961) 803
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KETY S Determinants of tissue oxygen tension Fed Proc 16 (1957) 666
KOLSTAD P Vascularization oxygen tension and radiocurability in cancer of the cervix Universitetsforlaget Oslo 1964
MOTTRAM J A factor of importance in radiosensitivity of tumors Brit J Radiol 9 (1936) 606
SCANLON P Split dose radiotherapy following in 50 cases Amer J Roentgenol 90 (1963) 280
THOMLINSON R Oxygen therapy biological consideration In Modern trends in radiotherapy p 68 Butterworth London 1967
— and GRAY L The histological structure of some human lung cancer Brit J Cancer 9 (1955) 539
URBACH F and NEOLL W Effect of oxygen breathing on tumor oxygen measured polarographically J appl Physiol 13 (1958) 61

SUMMARY

Changes in tumor oxygenation during radiation therapy were studied in sixty eight cases of lymphomas and carcinomas A significantly lower oxygenation compared to normal tissue in the tumor bed was observed in all the tumors The split course seemed to give the highest improvement in tumor oxygen tension in carcinomas A positive correlation was found between poor initial oxygenation and persistent tumor after irradiation with an initial critical oxygen tension of about 15 mm Hg It was concluded that the fractionation technique used can influence the clinical response in hypoxic tumors

ZUSAMMENFASSUNG

Veränderungen der Sauerstoffspannung in Tumoren während Strahlenbehandlung von Lymphomen und Carcinomen wurden in achtundsechzig Fällen studiert Im Vergleich mit normalen Geweben wurde in diesen Tumoren eine signifikant niedrigere Gewebssauerstoffspannung observiert Es scheint als ob bei der Behandlung von Carcinomen Dosisfraktionierung die grosste Verbesserung der Sauerstoffspannung hervorbringen durfte Eine positive Korrelation zwischen einer anfänglich niedrigen Sauerstoffspannung und persistierendes Tumorgewebe nach der Strahlenbehandlung wurde bei einer anfänglich kritischen Sauerstoffspannung von ungefähr 15 mm Hg konstatiert Daraus folgt dass in Fällen von Tumoren mit Sauerstoffmangel die gegenwärtige Technik von Dosisfraktionierung die klinische Reaktion beeinflussen durfte

RÉSUMÉ

Les auteurs ont étudié les modifications de l'oxygénation de la tumeur au cours du traitement par les radiations dans 68 cas de lymphomes et de carcinomes Dans tous les cas l'oxygénation du lit tumoral était significativement inférieure à celle des tissus normaux C'est le traitement fractionné qui paraît donner la plus grande amélioration de la tension d'oxygène tumorale dans les carcinomes Les auteurs ont trouvé une corrélation positive entre une faible oxygénation initiale et la persistance des tumeurs après irradiation avec une tension d'oxygène initiale critique d'environ 15 mm de Hg Ils concluent que la technique de fractionnement utilisée peut influer sur le résultat clinique dans les tumeurs hypoxiques

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Report on the Meeting of the International Commission on Radiological Protection (ICRP)

April 1969

The Commission decided to issue the following amendments to its recommendations that appeared in ICRP Publication No. 9

Dose limit to the lens of the eye In its most recent recommendations (ICRP Publication 9, paragraph 25) the *Commission included the lenses of the eyes amongst the most* radiosensitive tissues when exposed to radiations of high LET. The Commission therefore recommended the use of a special modifying factor for irradiation of the lenses of the eyes (paragraph 16).

A recent review by an ICRP Task Group to consider the relative radiosensitivities of *different tissues (ICRP Publication 14) concluded*

The human evidence suggests that the annual dose limit for exposure of the lens of the eye should be 15 rems for both low and high LET radiation. There is no need for the additional modifying factor used at present when QF > 1

The Commission endorses this conclusion of the Task Group and recommends that the dose limit for the lens of the eye be 15 rems *without the use of an additional modifying* factor.

Quality factor for β, β and e radiations with maximum energy ≤ 0.03 MeV

In ICRP Publication 9, paragraph 17, the Commission recommended a value of 1.7 as being the appropriate quality factor for β, β and e radiations with maximum energy ≤ 0.03 MeV. The Commission has reviewed the biological and physical evidence related to this point and concludes that a value of unity is appropriate within the degree of precision required for the purposes of radiological protection. The Commission therefore recommends that QF be taken as 1 for all β, β, e, γ and X radiations and for conversion electrons.

F. D. Sowby
Scientific Secretary, ICRP

Book reviews

TUMOURS OF THE THYROID GLAND (Les tumeurs du corps thyroide) Edited by A Appaix 468 pages with 130 figures and 73 tables S Karger Basel 1966 Price 75 SFR/DM

The volume contains papers presented at the international colloquium on 'Tumours of the thyroid gland' in Marseilles 1964 and brought up to date by the authors Most of the best known authorities of the western world on the subject have taken part and papers with opposing views have been paired deliberately whenever possible in order to animate the discussion

The tumours are discussed from virtually every aspect and a comprehensive picture of our present knowledge emerges from the well balanced presentation Among the more interesting problems considered are the lateral aberrant thyroid the plurifocality of papillary carcinoma the hormonal dependency of carcinoma of the thyroid the indications for lobectomy of the thyroid radical and supraradical thyroidectomy cervical dissection and operative techniques Such complications as paresis of the recurrent nerve and hypoparathyroidism find due place Large series are presented by experienced surgeons

A uniform clinical and pathologic classification is proposed by P Denoix and R Gerard Marchand of Villejuif

The usefulness of ^{131}I in the diagnosis and treatment of carcinoma of the thyroid and metastases is discussed in great detail

A fixed relationship between chronic thyroiditis and thyroid carcinoma has been established in a series of 436 patients by Hirabayashi & Linsay San Francisco who regard chronic thyroiditis as a precancerous condition

The results of treatment (surgery hormones, radiotherapy) are presented in a large well documented series and etiologic factors such as heredity hormones ionizing radiation are discussed and evaluated Certain interesting new diagnostic tools such as histophotometry and studies of the secretory activity of carcinoma of the thyroid are described

The numerous excellent illustrations and the comprehensive bibliography add to the usefulness of the volume which can be warmly recommended to all interested in problems connected with carcinoma of the thyroid

B Jereb

PROGNOSTIC FACTORS IN BREAST CANCER Proceedings of First Tenovus Symposium Cardiff 12—14 April 1967 Edited by A P M Forrest and P B Kunkler 481 pages 163 figures and 148 tables E & S Livingstone Edinburgh and London 1968 Price 70 shillings

The some 40 papers forming this book were presented at an international symposium attended by about a hundred specialists from different research centres Both those engaged in practical work with this type of malignant disease and those interested in the problem

theoretically should find the book of great value. It is well edited and although many different aspects are treated it is concentrated. The carefully assembled reference lists help the reader to obtain a good survey of the current literature in the different fields of research without loss of time.

The significance of well known etiologic factors such as fertility, pregnancy, number of children and breast feeding is discussed, and attention is also drawn to the variation in the natural course of the disease in untreated patients and in different forms of mammary carcinoma. The new epidemiologic investigations that have demonstrated the hitherto little known part played by dietetic factors in the occurrence of the condition are of particular interest. Tissue culture and clinical studies have also been undertaken to find out which form of hormone therapy is the most effective and which types of tumour respond to hormone treatment. Determination of androgen excretion in the urine and measurement of cortisol and of growth hormone in serum, especially in connection with glucose and insulin loading, have proved valuable. Direct measurement of hormones in blood serum with the aid of radio-immunity methods is being increasingly used in this field and has already resulted in considerable improvements in our knowledge of the connection between cancer and hormones.

The importance as well as the difficulty of teaching women to examine their breast regularly and the value of health controls with palpation and mammography have received fresh emphasis in new investigations. It was realized earlier that the detection of small primary malignant nodules can improve the results of treatment, but the main problem in this connection lies in the personal and economic stakes involved.

On the subject of tumour biology the significance of growth rate and growth pattern in different types of carcinoma is emphasized. Several investigators have demonstrated the value of histologic grading and clinical staging in the treatment of the disease and in the assessment and comparison of different treatment results. Operation of the primary growth is widely recommended for the management of operable cases; the value of exeresis axillae and postoperative irradiation as a measure for prolonging the survival time is however also discussed. Different opinions are expressed regarding the value of prophylactic and curative hormone therapy and endocrine surgery. Attention is also paid to immunity factors and to the problem of whether they are influenced by surgery, irradiation, hormones or cytostatic drugs.

The book offers lucid information on the varied problems connected with mammary carcinoma and can be recommended to those interested in its diagnosis and treatment.

Gustaf Notter

MALIGNANT TUMOURS OF THE THYROID GLAND. By F. Beregi, R. Jankovics and Z. Br..ch. 81 pages, 50 figures and 13 tables. Akadémiai Kiadó, Budapest 1967. Price 6 dollars.

The authors discuss the incidence, diagnosis, factors influencing the development, pathology, prognosis and treatment of malignant tumours of the thyroid in six chapters. The peculiar biologic behaviour of carcinoma of the thyroid and the difficulties in the differential diagnosis between malignant and benign thyroid tumours are described. The authors' own histologic classification is presented. The material consists of 198 malignant thyroid tumours (out of 11 122 strumectomies), 17 of which were lost to follow up. The influence of the age of the patient on the prognosis is stressed.

The book is not easy to read perhaps because the material and the discussion both seem to be somewhat disjointed Quite a few conclusions are conjectural and certain obvious facts are unduly emphasized The translation is often awkward with the result that the meaning is not always clear The book is nicely produced

B Jereb

CLINICAL AND RADIOBIOLOGICAL PROPERTIES OF MELANOBLASTOMA By I Rodé 302 pages 160 figures 27 tables Akadémiai Kiadó Budapest 1968 Price 14 70 dollars

The author a clinical radiologist with twenty years clinical experience of this tumour presents a material of 600 cases of melanoblastoma in different parts of the human body the most frequent localization being the skin Melanoblastomas occurred between the fourth and sixth decade in 63 per cent of the cases The author believes that specific developments pathologic cytologic biochemical and endocrinologic aspects of melanoblastomas raise particular biologic and oncologic questions

The book is divided into a general and a special part The general part discusses the nature and the physiologic and pathologic roles of melanin as well as experimental tumours in animals, and considers the clinical aspects of spontaneous melanuria The special part deals with melanoblastomas of the skin both from the view of general individual properties treatment and prognosis One chapter of this is devoted to problems arising in melanoblastomas of the eye and the central nervous system as well as in melanoblastomas lying in the genitalia digestive tract oral and pharyngeal cavities and other regions

A good bibliography is included at the end of the book and may encourage further study of this important tumour

Folke Edsmyr

RADIUM DOSAGE THE MANCHESTER SYSTEM Second edition Edited by W J Meredith 13? pages 38 figures 4 plates 21 tables 2 appendices with tables Livingstone London 1967 Price 42 shillings

The revised edition of this well known work is again in two parts Part I gives the basic rules and dose calculation methods of the Manchester System for radium and radon treatments originally developed by Paterson and Parker in a practical and useful manner A number of worked-out examples for the main types of treatment (moulds of various types line sources and implants) are included and the Manchester system of treatment of carcinoma of the cervix is also described This part contains everything needed in the daily work The numerical tables for the calculations are printed at the end of the book on fold-out sheets which may easily be consulted while the text pages are perused

Part II deals with the scientific foundations of the methods It consists of essentially unchanged reprints of a number of papers of several authors over the period 1934—1953 in which the physics of the system are developed the basic formulas are derived and the suitability of the rules given in part I are proved This method of presentation entails some formal inconsistences such as the use in the earlier papers of the term intensity and later dosage rate for the quantity now known as exposure rate This should however cause little serious confusion to the attentive reader

Part II also contains a useful chapter on radiography for checking the needle positions in implants and a concluding chapter on A new unit and some new sources that explains the conversion of exposure in R to dose in rad and on dosage calculations for certain artificial gamma emitters An appendix indicates how calculations may be made in situations not covered by the planar mould or line source tables

This new edition will be heartily welcomed in the many radiotherapy centres all over the world where the Manchester system is in use The book is however also recommended to radiotherapists and physicists who do not employ it Familiarity with such an extensively used system is valuable for comparison with others and for judging their relative merits The general approach is also well worth studying Many of the numerical data and the information in the chapters on radiography position control as well as on the new unit and new sources may be more or less directly applied to other systems

Sten Benner

RADIOATOMS IN NUCLEAR MEDECINE By P H Blichert Toft 78 pages 47 figures Gothenburg Press Vårmånadsgatan 5 B Goteborg 1968 Price Sw Kr 25

This monograph presents decay schemes radiation types and energies for a number of medically interesting radionuclides A few omissions e g [illegible]Co and ^{133}Xe and above all the iodines will it is hoped be included in a second edition The material is based on a critical survey and selection from the large amount of data in the literature The many papers used have not been quoted explicitly but appear under the reference codes of the Nuclear Data Group of the Oak Ridge National Laboratory *This has saved space although readers* wanting to consult the original papers and without the group publications at hand may find this somewhat inconvenient

Many radiologic physicists will welcome the collection of all these data in a handy little volume instead of having to search for them in the extensive literature or in bulkier hand books when wanting to perform dosage calculations designing protection screens etc Many radiologists may however be unable to gain the utmost from the book because of in sufficient background in nuclear physics

Sten Benner

ACTA RADIOLOGICA

OFFICIAL ORGAN OF THE RADIOLOGICAL SOCIETIES OF
DENMARK FINLAND NORWAY AND SWEDEN

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EFFECTS OF PROTON AND ROENTGEN RADIATION ON THE RECTUM OF THE RAT

by

STIG STENSON

The maximum dose of proton or roentgen radiation that can be given to uterine carcinomas is determined by the reaction of the pelvic organs, particularly the rectum (TODD 1938 INGELMAN SUNDBERG 1947) KOTTMEIER & GRAY (1961) and KOTTMEIER (1964a) reported that a total dose of more than 6 000 R given by the Stockholm method (cf KOTTMEIER 1964b) to the rectum frequently produces injury to the mucosa Serious rectal injuries such as proctitis and recto-vaginal fistulas have been caused when uterine carcinomas were treated with single or fractionated doses of high energy protons (FALKMER et coll 1962 FORS et coll 1964)

STENSON (1969) compared the ability of 185 MeV protons and 220 kV roentgen rays to cause weight changes and mortality in rats after abdominal irradiation A relative biologic efficiency (RBE) of 0 75 ± 0 18 for the protons as compared with the roentgen rays was recorded No detailed histologic study was performed however

In the present study only a small part of the abdomen of the rats was ir

From the Department of Radiobiology at the Gustaf Werner Institute the Department of Gynaecologic Radiotherapy University of Uppsala and the Institute of Pathology II University of Umea Sweden

Submitted for publication 18 April 1969

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uncertainty in the dose values was estimated to be 5 % for protons (cf LARSSON 1962) and 10 % for roentgen rays (CEDERLUND 1967) After irradiation the rats were individually marked in the ears five or six kept together in a cage given food and water ad libitum and checked daily for signs of radiation damage One third of the rats at each dose level were killed at 8 days one third at 28 days and the rest if possible at one year They were killed without anaesthesia and a post mortem examination was performed immediately The macroscopic findings were recorded and specimens taken for microscopic investigation

Radiologic techniques

The *proton irradiation* was administered with the 185 MeV proton beam of the 230 cm synchro-cyclotron the cross-section of which was a 2 5 cm × 4 cm rectangle The dose rate was 300 to 800 rad/min and the homogeneity of the beam was determined as described by FALKMER et coll (1959) The mean flux density of the beam over the rectal area was in the range ± 5 %

The anaesthetized rats lay dorsally on a wooden support during the irradiation and were aligned in the beam by means of external landmarks The alignment was checked roentgenographically in 19 instances (Fig 1) and in these small corrections had to be made twice The beam passed through the rat from side to side and a 2.5 cm wide segment of the lower abdomen was irradiated

The beam was used without intervening absorbers the energy of the protons being about 170 MeV at the level of the rectum The position of the animal was controlled on a TV monitor during the irradiation

The *roentgen irradiation* was performed at the Department of Radiotherapy University of Uppsala The factors were 220 kV 1 mm Al filtration and a focus-skin distance of 30 cm to produce a surface dose rate of 340 rad/min The dose rate was determined by means of an ionization chamber (Philips type 37480/10) The rectal dose was 79 % of the surface dose as determined by a miniature ionization chamber placed in the rectum

During irradiation the anaesthetized rat lay dorsally on a 2 5 cm thick wooden platform covered by a 5 mm lead sheet having an opening of 2 5 cm × 5 cm over the lower part of the abdomen (Fig 2) The landmarks for alignment were the same as those used for the proton irradiation the animals were observed through a window

Histopathologic study The animals lay as for irradiation specimens being taken from irradiated parts of the rectum and other organs by means of the same external landmarks as previously These were fixed in 10 % formalin dehydrat



Fig. 1. Lateral roentgenogram showing the position of the rectangular proton field.

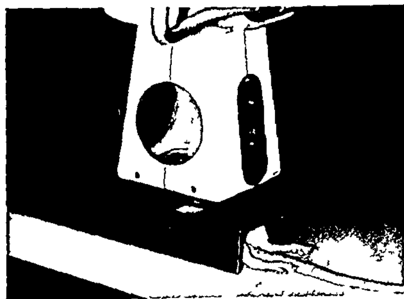


Fig. 2. Set up for the roentgen irradiation.

radiated, so as to permit a long term histologic investigation and to enable a comparison between changes in the rectum induced by these two types of radiation.

Material and Methods. The pelvic region of 120 female rats of the strongly inbred Sprague Dewley strain, 6 to 8 weeks old, of 210 ± 23 g mean body weight, were irradiated, 75 rats with protons (P rats) and 45 rats with roentgen rays (X rats). The P rats and the X rats were each divided into five groups, one for each dose level. The rats were anaesthetized with nembutal (Abbott), 4 mg/100 g body weight intraperitoneally. The P rats received single doses of from 1 100 to 2 420 rad and the X rats single doses of from 900 to 1 800 rad. The

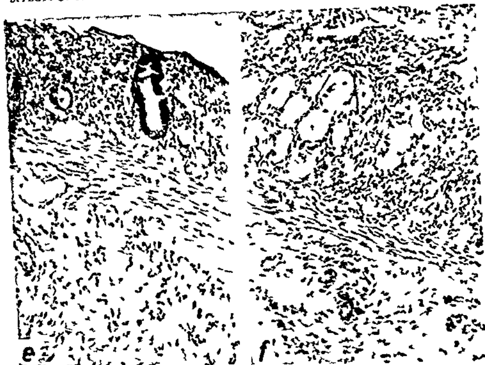


Fig 3 (see also opposite page) Photomicrographs showing the various degrees of radiation induced histologic changes in the rectal wall of rats Hematoxylin eosin or van Gieson's stain Magnification 135

a) (opposite page) Grade 0 Normal rectal wall with long straight crypts of Lieberkuhn narrow lumina *and high columnar* goblet cells apparently actively secreting a lymph follicle (center right) lies between the muscularis mucosae (middle) and the muscularis propria (bottom)

b) (opposite page) Grade I+ The lumina at the bottom of some of the crypts of Lieberkuhn are slightly widened (*top center*) apparently due to shrinkage of some of the epithelial cells

c) (opposite page) Grade II+ Atrophy of the columnar goblet cell epithelium in the crypts of Lieberkuhn exaggerated by the formation of slightly cystic lumina (top center)

d) (opposite page) Grade III+ Most of the epithelial mucosa is flattened or desquamated leaving only small cystic remnants of the *crypts surrounded* by inflammatory cells the surface epithelium (top) is considerably altered by polymorphism and hyperchromasia moderate oedema of the submucosa layer (bottom)

e) Grade IV+ The mucosa (top) is thin surface epithelium is absent or markedly atrophic and only single isolated epithelium lined crypt like *structures occur* the submucosa is markedly oedematous and invaded by inflammatory cells

f) Grade V+ No epithelial structures occur in the atrophic mucosa (center) which is covered by a fibrinous membrane containing granulocytes and cellular debris (top) Most of the mucosa is converted *into cellular* granulation tissue containing small pools of mucin inflammatory cells of the markedly oedematous submucosa (bottom) encroach upon the muscularis propria (not shown) producing phlegmonous inflammation of the *rectal wall*

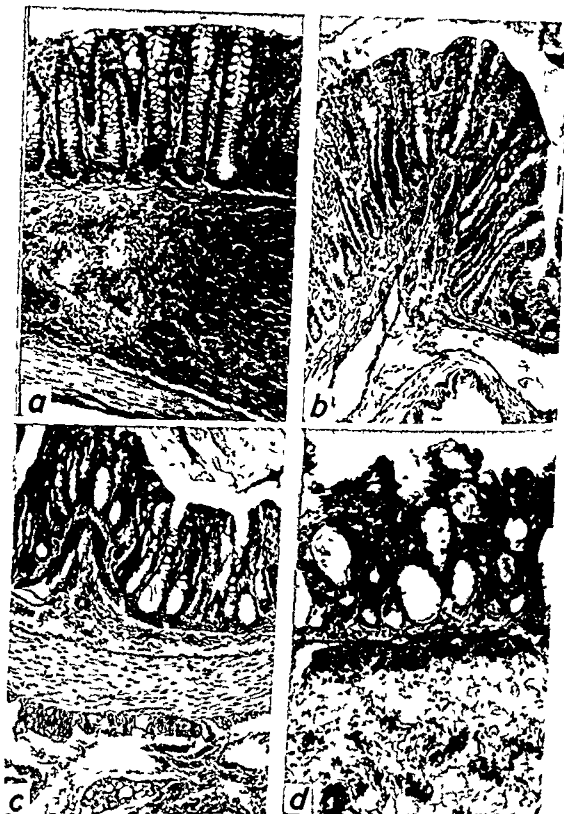


Fig 3 (see opposite page)

Table 2

Post mortem findings in rats sacrificed 8 days after irradiation — For microscopic grading O to V + see Table 1 and Fig 3

Dose rad	Rat No	Gross inspection	Microscopic study
A Proton irradiated rats			
1 100	1	Normal	0
	2	Normal	0
	3	Normal	0
	4	Normal	0
	5	Normal	0
1 380	1	Normal	0
	2	Normal	0
	3	Normal	0
	4	Normal	0
	5	Normal	0
1 660	1	Normal	+
	2	Normal	++
	3	Normal	++
	4	Normal	+
	5	Normal	+
1 930	1	Normal	++++
	2	Normal	++++
	3	Normal	++++
	4	Normal	++++
	5	Normal	+++
2 210	1	Normal	++++
	2	Adhesions in pelvis	+++++
	3	Swelling of rectal wall	+++
	4	Swelling of rectal wall	++++
	5	Normal	++++
B Roentgen irradiated rats			
900	1	Normal	0
	2	Normal	0
	3	Normal	0
1 125	1	Normal	++++
	2	Normal	+++
	3	Normal	+++
1 350	1	Normal	++
	2	Normal	++++
	3	Normal	++++
1 575	1	Normal	+++++
	2	Normal	+++++
	3	Normal	+++++
1 800	1	Swelling of rectal wall	+++++
	2	Swelling of rectal wall	+++++
	3	Swelling of rectal wall	+++++

Table I

Principal histologic criteria in the semiquantitative classification of radiation induced changes in the rectum of rats used in the experiments

Grade	Surface epithelium	Goblet cells in the crypts	Width of crypts	Height of mucosa	Sub mucous layer	Muscularis propria
0	High columnar regular	High columnar regular actively secreting	Narrow	Normal	Normal	Normal
I+	High columnar regular	Slight irregularity atrophy and slightly reduced secretion	Slight widening in the bottom of some crypts	Normal	Normal	Normal
II+	High columnar regular	Marked atrophy especially at the crypt bottom	Most crypts clearly widened	Normal	Normal	Normal
III+	Irregular with hyperchromatic polymorphous cells	Most of the cells atrophic or desquamated	Markedly cystic	Normal	Oedema	Normal
IV+	Mostly absent or markedly atrophic	Only small epithelial remnants	Mostly absent	Moderately reduced	Oedema	Normal
V+	Absent (substituted by fibrinous membranes)	Absent	Absent	Moderately reduced	Oedema	Mostly invaded by inflammatory cells

ed, cleared and embedded in paraffin The sections were cut about 5 μ thick and stained with haematoxylin eosin or van Gieson s stain, those from the rectum were mostly cut longitudinally Sections presenting no damage indicated that the specimens had to be investigated by serial section The criteria for the histologic grading are given in Table 1 and Fig 3 The sections were assessed unknown and independently several times by two investigators The variations between individual gradings were small and the final assessment was easily adjusted

Results

Gross changes especially in the rectum and the bladder, were evident post mortem Swellings of the walls of the rectum or bladder, stricture and circumscript dilatation of the rectum, and adhesion between the organs, were classified

as radiation induced changes The results of the gross observations are given in Tables 2 3, 4 and 5 for the three different observation periods together with the microscopy findings in specimens taken from the irradiated part of the rectum.

The structure of the surface epithelium of the mucous membrane and the goblet cells in the crypts the width of the crypts and the height of the mucosa the structure of the submucosa and the muscularis propria of the rectal wall were all studied Fibrosis was also recorded The principal histologic criteria used in the semiquantitative classification of the radiation induced changes in the rectum of the rats appear in Table 1 The photomicrographs in Fig 3 indicate the grading of the radiation induced histologic changes in the rectal wall

The 8-day groups All the animals in these groups survived the observation period Post morten examination revealed gross swelling of the rectal wall in two of the 2 210 rad P rats In another 2 210 rad P rat there were adhesions in the pelvis and in three 1 800 rad X rats swelling of the rectal wall had occurred The remainder of the animals in the 8 day groups presented no gross changes post mortem The microscopic investigation of specimens from the irradiated part of the rectum revealed no radiation induced damage in the 1 100 and 1 380 rad P rats but all the 1 660 rad P rats had grade I—II changes The 1 930 and 2 210 rad P rats had grade III—V damage Roentgen irradiation of 900 rad produced no visible damage but a dose of 1 125 rad led to grade III—IV a dose of 1 350 rad to grade II—IV and doses of 1 575 and 1 800 rad to grade V damage in all the animals

The 28 day groups Three of the 40 rats died within the observation period one 1 450 rad P rat from pneumonia 6 days after irradiation one 2 030 rad P rat from obvious radiation sickness (marked weight loss and diarrhoea with blood tained stools) 9 days after radiation and one 1 575 rad X rat 17 days after irradiation from radiation sickness (weight loss and diarrhoea with blood stained stools) The surviving 37 rats were sacrificed 28 days post irradiation gross examination revealing swelling of the rectal wall in three of the P rats and in one of the X rats The microscopic examination revealed no damage in the 1 160 rad and 1 450 rad P rats or in the 900 rad X rats and only slight changes in the specimens from the 1 740 rad P rats and the 1 125 rad X rats The 2 030 rad P rats had grade I—II damage and the 2 320 rad P rats had grade III—IV damage. In specimens from the 1 350 1 575 and 1 800 rad X rats there was mostly grade III—V damage

The 1 year groups All the 1 470 rad and 1 760 rad P rats survived one year as did all the 1 180 rad P rats but one which apparently died from a large

Table 3

Post mortem findings in rats sacrificed 28 days after irradiation — For microscopic grading 0 to I +, see Table 1 and Fig 3

Dose rad	Rat No	Gross inspection	Microscopic study
1 Proton irradiated rats			
1 160	1	Normal	0
	2	Normal	0
	3	Normal	0
	4	Normal	0
	5	Normal	0
1 450	1	Normal	0
	2	Normal	0
	3	Normal	0
	4	Dead from pneumonia on day 6 Post mortem changes	—
	5	Normal	0
1 740	1	Normal	+
	2	Normal	0
	3	Normal	+
	4	Normal	+
	5	Some swelling of rectal wall	0
2 030	1	Haemorrhagic diarrhoea weight loss 50 g dead from radiation sickness on day 9	—
	2	Normal	++
	3	Normal	++
	4	Swelling of rectal wall	+
	5	Normal	++
2 320	1	Normal	+++
	2	Normal	+++
	3	Swelling of rectal wall	++++
	4	Normal	++++
	5	Normal	++++
B Roentgen irradiated rats			
900	1	Normal	0
	2	Normal	0
	3	Normal	0
1 125	1	Normal	0
	2	Normal	+
	3	Normal	+
1 350	1	Normal	+++++
	2	Normal	++
	3	Normal	+++
1 575	1	Normal	+++
	2	Normal	+++
	3	Haemorrhagic diarrhoea weight loss 54 g dead from radiation on day 17	—
1 800	1	Normal	0
	2	Swelling of rectal wall	++++
	3	Normal	+++++

Table 5

Post mortem findin s in roentgen irradiated rats which were sacrificed 1 year after irradiation or died during the observation period — Survival time in days given in parentheses — For microscopic grading O to I + see Table 1 and Fig 3

Dose rad	Rat No	Sacrificed (S) Died (d)	Gross inspection	Microscopic
900	1	d (319)	Death from pneumonia post mortem changes in pelvis	0
	2	S (365)	No mal	0
	3	d (319)	Death f om pneumonia no radiation induced changes	0
1 125	1	d (346)	De th f om pneumonia no rad at on induced changes	?
	2	d (337)	Death from pneumonia no rad ation induced changes	++
	3	d (305)	Death f om pneumonia adhes ons between organs in pelv s	?
1 350	1	d (26)	Death from radiation we ght lo s 37 g blood in stools post mortem changes	—
	2	d (42)	Death from radiation we ght lo s 24 g adhes ons in pel is ileus	—
	3	d (334)	Death f om ileus caused by tumour of intestine rectum apparently normal	+
1 575	1	d (10?)	Death from irradiation rectum d lated ureters dilated p rt of intest ne blue red	—
	2	d (10?)	Death from irradiation str cture of rectum small intes tine d lated	—
	3	d (77)	K lled by the other rats in cage in bad condit on foll ow ng irrad ation	—
1 800	1	d (7)	Death with signs of acute intest nal radiation s ckness	—
	2	d (7)	Death w th signs of acute ntestinal radiation sickness	—
	3	d (6)	Death with s gns of acute intestinal rad ation sickness	—

aesthetic on the day after irradiation and one from a large tumour on the right leg 317 days after irradiation Four months after treatment the remaining rat in this group developed septic ulceration of the irradiated part of the right hind leg and this rat obviously dying from the infection was sacrificed 211 days after irradiation No rat in this group had any gross radiation induced damage in the pelvis Four of the 2 420 rad P rats died from radiation induced damage The first died after 158 days and post mortem examination indicated that the small intestine was dilated and filled with haemorrhagic fluid there was also blood in the peritoneal cavity The second rat died 190 days after irradiation The rectum the bladder as well as the ureters were dilated and the rat probably died from uremia and an ileus The third and the fourth rats died from rectal perforation on days 205 and 304 respectively The last rat in this group developed serious infection of the irradiated skin and in order to obtain a representative specimen

Table 4

Post mortem findings in proton irradiated rats which were sacrificed 1 year after irradiation or died during the observation period — Survival time in days given in parentheses — For microscopic grading 0 to ++++ see Table 1 and Fig 3

Dose rad	Rat No	Sacrificed (S) Died (d)	Gross inspection	Microscopic
1 180	1	S (365)	Normal	0
	2	S (365)	Normal	0
	3	S (365)	Normal	0
	4	d (352)	Cystic blood filled tumour at vulva death from the tumour (?) post mortem changes in pelvis	—
	5	S (365)	Abscess of left hind leg no radiation induced damage to pelvis	0
1 470	1	S (365)	Normal	0
	2	S (365)	Normal	0
	3	S (365)	Normal	0
	4	S (365)	Normal	0
	5	S (365)	Normal	0
1 760	1	S (365)	Normal	+
	2	S (365)	Normal	+
	3	S (365)	Normal	+
	4	S (365)	Normal	+
	5	S (365)	Normal	+
1 920	1	S (365)	Normal	+
	2	d (1)	Death from the anaesthetic	—
	3	S (365)	Normal	+
	4	d (317)	Hard 62 g tumour in right hind leg death from the tumour (?) post mortem changes in pelvis	—
	5	S (211)	The irradiated skin necrotic sacrificed in very bad condition for obtaining representative specimens normal	+
2 420	1	d (205)	Rectum dilated and perforated small intestine dilated death from irradiation induced changes	—
	2	d (190)	Rectum bladder and ureters dilated death from irradiation	++
	3	d (158)	Small intestine dilated and filled with blood stained liquid perforation death from irradiation	++
	4	S (206)	Sacrificed because of serious infection of irradiated skin rectum and bladder thick and pale	+
	5	d (304)	Rectal perforation from irradiation	+++++

blood filled cystic tumour near the vulva 352 days after irradiation *Post mortem* examination revealed no radiation induced damage in the rectum of the rats in these three groups One of the 1 180 rad P rats had an abscess in the irradiated part of the left hind leg

Of the 1 920 rad P rats two survived one year, one rat died from the an

crypt cells stops for 12 hours and during the following 36 hours it is abnormal and scanty and obviously fails to keep pace with the cells that are degenerating Under these conditions the cells of the villi increase in life from 1 3 to 2 days an effect which is unlikely to be caused directly by the irradiation They present no visible injury within 48 hours but after 48 to 96 hours become mis-shapen, laden with lipid and finally slough When the mitotic activity of the crypt cells decreases the cells of the villi are not crowded out by new cells arising from the crypts and they die in situ the degeneration of cells beginning at the tip of the villi Later degenerated cells may be found half way down the side of the villi and after 96 hours all the cells in the villus are degenerated The disparity in the damage to different parts of the intestines may reflect differences in the rate at which the cells of the villi are normally replaced Damage is greatest in the duodenum less in the ileum and still less in the caecum (MONTAGNA & WILSON 1955)

Information about radiation damage to the rectum is less concise It is clear, however that the mechanism of cell renewal in the rectum is similar to that in the small intestine irrespective of the fact that the rectum contains no villi and that the cell turnover time is 6 2 days (BERTALANFFY & LAU 1962) The results of the present investigation indicate that the radiation doses used cover the range from no apparent to fatal damage

In the grading of the radiation damage the lower grades (I+ to II+) refer to changes in the crypt cells and to the crypts themselves If the crypt damage is serious (grade III+ to V+) this will later become apparent in the mucous epithelium which will be destroyed and create an ulcer in the mucosa a failure to heal will then produce perforation of the rectal wall If healing takes place the epithelium will regenerate from the mucosal remnants around the ulceration and fibrotic scarring may occur in the submucous and muscular layers. Apparently most animals with grade V damage died within one year of irradiation

The observation periods were chosen so as to make it possible to study the development and repair of the radiation induced damage of the rectum acute damage at 8 days repair of the rectal wall at 28 days and chronic changes at one year

Post mortem examination of the sacrificed 8-day rats revealed slight gross changes even at the highest doses The microscopic changes were of greater interest Doses of 1 660 to 2 210 rad of protons produce gradually increasing damage to the rectal wall and the same changes occur after 1 125 to 1 800 rad of roentgen rays It seems that roentgen rays have a greater ability to induce acute damage to the mucous membrane of the rectal wall than the protons but there are no significant qualitative differences between the changes evoked The proton dose needed to induce a grade IV damage is 1 930 rad the corresponding roent

from the rectum, the rat was sacrificed 206 days following irradiation The post-mortem examination revealed a pale, thickened wall of the rectum and the bladder Thus, no rat in this 2 420 rad proton group survived the observation period of one year

Five of the X rats of the 900 and 1 125 rad groups died from pneumonia 305 to 346 days after irradiation, no radiation induced changes were evident post mortem in the pelvis except in one rat which had adhesions between the bladder and the rectum One 900 rad X rat survived the observation period and at post mortem examination there was no damage in the irradiated zone Two rats of the 1 350 rad X-group obviously died from radiation induced damage and one from ileus caused by a tumour in the small intestine the rectum was grossly normal in the latter Two of the 1 575 rad X rats died on day 102 from radiation induced damage, with loss of weight, diarrhoea, and marked epilation of the irradiated skin The post mortem examination in one of these rats revealed marked dilatation of the irradiated part of the rectum, and in the other stenosis of the rectum with dilatation of the oral part of the intestine The third rat in this group was probably killed because of its condition by the other rats 77 days after irradiation, the intestines were dilated and the rectum was eaten away before investigation The three rats in the 1 800 rad X group all suffered from haemorrhagic diarrhoea weight loss of 50 to 60 g and died 6 to 7 days after treatment The post mortem revealed dilated, blue red intestines filled with blood stained fluid in the lower abdomen These three rats all died from radiation induced damage

Microscopy of specimens from the rat that survived one year disclosed no serious damage to the rectal wall Post mortem changes were usually present in the mucous membrane of the rats that died during the observation period but the rectal wall was clearly fibrotic The grading of the irradiation induced damage was difficult in these cases the gross examination gave a better basis for estimation of the changes created by the irradiation

Discussion

The acute changes induced by ionizing radiation in the mucous membrane of the small intestine of the rat are well known (QUASTLER 1956) Most authors agree that the critical damage occurs in the mitotically active cells of the crypts, which are fatally damaged by a dose of 1 000 rad After maturation and migration up the wall of the villi the epithelial cells can be exposed to 30 000 rad, and probably more, without fatal effects (QUASTLER 1959) The time required for a renewal of the epithelium of the villi is on an average 1 3 to 1 6 days (BERTALANFFY & LAU 1962) After irradiation with 1 000 rad, mitotic activity in the

proton dose of about 1 900 rad appeared to heal and the animals survived the treatment The corresponding critical dose for roentgen irradiation was probably 1 350 rad Damage to the rectal mucosa from slightly higher doses seemed to heal, at least partly but other types of changes in the rectal wall, the bladder or the ureters such as fibrosis and inflammation often killed the animal

Acknowledgement

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SUMMARY

A segment of the rat pelvis was irradiated with high energy protons or roentgen rays The ability of the two types of radiation to evoke damage of the rectum was compared by gross and microscopic examination eight days to one year later The results indicate that the two types of radiation create the same type of damage but that the protons seem to be slightly less effective

ZUSAMMENFASSUNG

Ein Segment des Rattenbeckens wurde mit Hochenergi protonen oder mit Rontgen bestrahlt Die Neigung zur Strahlenschadigung des Rektums bei den beiden Strahlung formen wurde mittels makroskopischer und mikroskopischer Unter uchung acht Tage bis ein Jahr spater verglichen Es ging von den Resultaten hervor dass die beiden Bestrahlungsmethoden die elben Schaden verur achen dass aber die Protonenstrahlung mildere Schad n hervorruft

RÉSUMÉ

Des rats ont subi l irradiation par des protons de haute energie ou par des rayonnements de roentgen d une partie de leur bassin Les lesions rectales dues à ces deux types de radiation ont ete comparees par des examens macroscopiques et microscopiques de huit jours a un an apres l irradiation Les resultats montrent que ces deux types de rayonnement donnent les memes types de lesion mais qu les protons semblent un peu moins efficaces

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gen dose being 1 350 rad (RBE 0.7), the doses creating no apparent damage are 1 380 rad for protons and 900 rad for roentgen rays (RBE 0.6).

Two of the rats in the 28 day groups died from obvious radiation sickness (weight loss and haemorrhagic diarrhoea), one 2 030 rad P rat on day 9 and one 1 575 rad X rat on day 17. The death of these two animals was probably due to the irradiation of a larger volume of the small intestine than in the other rats. The other rats in these two dose levels presented no sign of radiation sickness nor did the rats at the highest dose level. On microscopic examination, the degree of damage was less in the 28 day P rats than in the 8 day P rats at the same levels. The X rats, too, had a lower degree of damage at 28 days than at 8 days. At the highest proton and roentgen dose levels the damage evident at microscopy was of the same magnitude for both observation periods. Comparison of the damage at the different dose levels for proton and roentgen irradiation indicated approximate equivalence between a proton dose of 1 740 rad and a dose of 1 125 rad roentgen rays (RBE 0.6), and between a proton dose of 2 320 rad and a roentgen dose of 1 350 rad (RBE 0.7).

The examination of the 1 year rats irradiated with proton doses of 1 180 to 1 920 rad revealed no gross radiation induced changes in the pelvic organs and microscopically only grade I damage to the rectum from 1 760 to 1 920 rad. The effects of 1 920 rad and 2 420 rad doses differed considerably. The five rats in the latter dose group all died from radiation induced damage of the pelvic organs, three of them from rectal perforation. One rat had fibrosis of the ureters, bladder, and rectum and probably died from uremia. The last rat in this group had fibrosis of the bladder and the rectal walls. The serious damage of the rectal wall seen at 8 and 28 days after roentgen irradiation with 1 350 rad or more is apparently fatal. The critical roentgen dose was obscured by the pneumonia which killed the 900 and the 1 125 rad X rats during the observation period. However, the post mortem examinations revealed no radiation changes in these animals except in one that had adhesions in the pelvis. The 1 800 rad X rats died 6 to 7 days following irradiation from acute intestinal radiation sickness and the findings at microscopy were therefore of less interest.

A comparison in the 1 year groups between the ability of the two types of radiation to cause similar degrees of damage indicated that the highest proton or roentgen dose to produce no changes was 1 760 and 1 125 rad, respectively (RBE 0.6). The lowest doses to cause death of the animals were 2 420 rad of proton and 1 350 rad of roentgen radiation (RBE 0.6). Proton and roentgen irradiation thus created in the rectum of rat the same type of gross and microscopic radiation damage although there was a clear difference in efficiency. The relative biologic efficiency of the protons seemed to be 0.6 to 0.7. The acute damage to a relatively small area of the rectal mucous membrane from a single

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by

W JACKSON

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The expression for the effect of a change in FSD on the zero area depth dose is straightforward, being simply the inverse square factor F. With a beam of finite area, however, the scatter component introduces a difficulty in that the variation of scatter with focal distance is not known. If we accept that the factor F is close to unity we may rewrite $\frac{1+F}{2}$ as $F^{\frac{1}{2}}$. For, substituting $(1+a)$ for F where a is small we have $\frac{1+F}{2} = 1 + \frac{a}{2} \approx (1+a)^{\frac{1}{2}} = F^{\frac{1}{2}}$. In fact, it seems more fundamental to regard the depth dose variation as lying between F and $F^{\frac{1}{2}}$, and we therefore designate the variation factor as F^p, where the above findings suggest that $1 < p < \frac{1}{2}$. The problem is to find an expression for p which will hold for all depths, beam areas and qualities.

Formula for p

Consider a roentgen ray beam of surface air exposure E incident on a tissue equivalent phantom at focal distance f_1. The exposure at depth may be divided into its primary or zero area component a and scatter component Φ, giving as depth dose $\frac{a+\Phi}{E \times B_1}$, where B_1 is the backscatter factor for the focal distance f_1. Now let the focal distance be changed from f_1 to f_2, keeping the same surface field size and air exposure at the new FSD. If the scatter component varies as F^q, it follows that the new depth dose is $\frac{aF+F^q\Phi}{E \times B_1}$, the backscatter factor being the same for both focal distances.

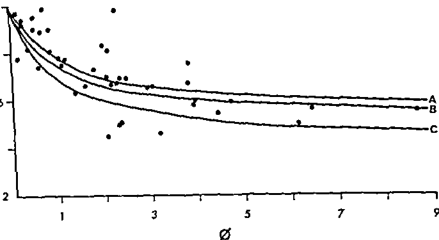
Thus $\frac{(\text{depth dose})}{(\text{depth dose})_1} = \frac{aF+F^q\Phi}{a+\Phi}$

Writing $\varphi = \frac{\Phi}{a}$, this becomes $\frac{F+\varphi F^q}{1+\varphi}$

This has been designated F^p, and so $F^p = \frac{F+\varphi F^q}{1+\varphi}$

The equation may be solved for p in terms of q and φ by writing $F = 1 + a$ and using the first term only in the binomial expansion of F^p and F^q. It gives

$$p = \frac{1+q\varphi}{1+\varphi}$$



g 1 Values of p v φ from published data composite points The curves are from the formula $p = \frac{1+q\varphi}{1+\varphi}$ with (A) $q=0\ 55$ (B) $q=0\ 50$ and (C) $q=0\ 40$

The error introduced by ignoring the second and subsequent terms in the binomial expansion is examined later and shown to be negligible The equation is the link which relates the index p with q which is easily obtained from the tables Since φ changes only slowly with focal distance its value at either focal distance may be taken when computing p The next step is to find a value for q i e the parameter representing the variation of scattered radiation with change in focal distance

Estimation of q

Both p and φ are readily available from published data for a given change in focal distance and since $q=\frac{p\ (1+\varphi)-1}{\varphi}$ it may be deduced for any depth dose It should therefore be possible to express it as a function of the parameters of depth or quality or beam area Unfortunately the accuracy of the published data is such that individual estimates of q derived in this way show a very large spread and so in the first instance an average value of q applicable to all conditions was obtained A wide range of φ values was available by appropriate choice of qualities beam areas and depths and for each φ a p was calculated

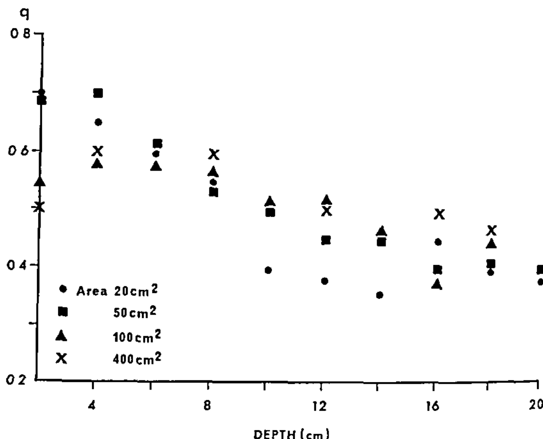


Fig 2 Computer values of q as a function of depth for 1 5 mm Cu HVT

for a particular change in focal distance Since one condition of quality, area, and depth gave a group of slightly differing p values for different focal distance changes, the centroid of the group was chosen and it is these composite points which have been graphed (Fig 1) The superposed curves are those from the formula $p = \frac{1+q\varphi}{1+\varphi}$ with $q = 0$ 4, 0 50 0 55 A best fit, chosen by least squares criterion, gave $q = 0$ 52

It was considered that it might be possible to smooth out the errors in published values of depth doses by the analysis of a sufficiently large quantity of data and hence to obtain the pattern by which q varies with depth, beam area, or quality An Olivetti Programma 101 Computer was employed and q s were evaluated for complete tables of published values in high energy (cobalt 60 gamma rays), a range of medium voltage roentgen rays (0 5, 1 5, 3 0, 5 0 mm Cu HVT) and soft roentgen rays (2 mm Al and 3 mm Al HVT) The data for 4 MV roentgen rays was discarded because of uncertainty in zero area dose and

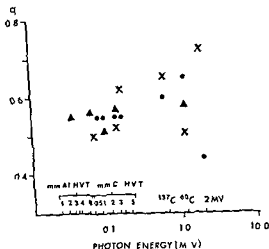


Fig 3 Values of q at 10 cm (●) and 20 cm depths (×) as derived from the ratio of values of φ at two FSD s Comparison with values from computer analysis of all areas (▲)

backscatter factor For cobalt 60 the 100 % dose was assumed to be at depth 0 5 cm and both depth and F factor were referred to this point

Except for a small range of medium voltage qualities — 0 5 mm Cu and 1 5 mm Cu HVT — where q fell from 0 65 at 2 cm depth to 0 4 at 20 cm (Fig 2), the results gave little evidence of any pattern of variation of q with the parameters mentioned In fact they seemed rather to indicate that any change would be small There was however positive evidence that q lay between fairly well defined limits — 0 4 to 0 7

A further possibility of testing the manner in which q varies with beam area arises from the fact that the ratio of φ values at two FSD s may be expressed as a function of q For if a is the zero area depth dose and Φ the scatter component we have for focal distances f_1 and f_2

$$\frac{\varphi_1}{\varphi_2} = \frac{\Phi_1}{\Phi_2}\,\frac{a_2}{a_1} = F^{-q} \times F = F^{1-q}$$

If then for a given depth φ is plotted against beam area for two different FSD s the value of q in terms of area may be derived from the ratio of the values of φ The method is useful in that the errors of published data are partially smoothed out in the graphical process It was applied first to the medium voltages which gave the most consistent results in the last method φ was computed at 10 cm depth for all the published areas and for focal distances 50 cm and 80 cm and from the two graphs the ratio of the values of φ was obtained as a function of area Apart from slight discrepancies for areas smaller than 50 cm²

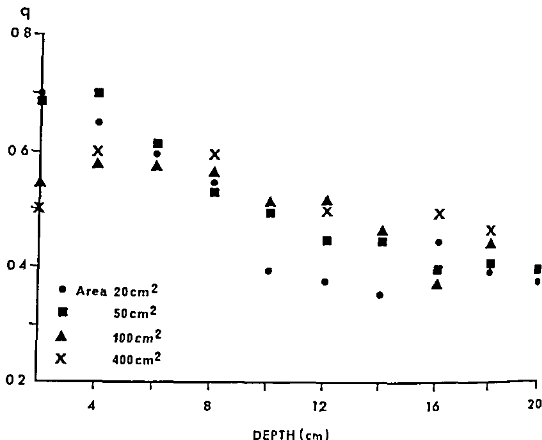


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It was considered that it might be possible to smooth out the errors in published values of depth doses by the analysis of a sufficiently large quantity of data and hence to obtain the pattern by which q varies with depth, beam area, or quality An Olivetti Programma 101 Computer was employed and q s were evaluated for complete tables of published values in high energy (cobalt 60 gamma rays), a range of medium voltage roentgen rays (0 5, 1 5, 3 0, 5 0 mm Cu HVT) and soft roentgen rays (2 mm Al and 3 mm Al HVT) The data for 4 MV roentgen rays was discarded because of uncertainty in zero area dose and

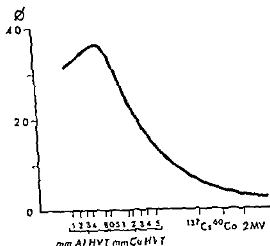


Fig 4 Variation of φ at 10 cm depth with energy beam area 100 cm

The position of this point may be calculated for different values of q Consider for example a variation of FSD from 50 to 60 cm a depth of 10 cm and a q of 0 4

$$\text{Then} \left(\frac{60}{60+\bar{x}} \cdot \frac{50+\bar{x}}{50}\right)^2 = \left(\frac{36}{35}\right)^{0\,8}$$

which puts it at a distance $\bar{x}=3\,6$ cm below the surface The fact that this effective zone centre is so near the surface tends to discount q values much lower than 0 4 High values put the centre close to P itself—$q = 0\,8$ gives $\bar{x} = 7\,7$ cm and there seems no reason to doubt that this could be realized for soft radiations where not only is the zone size reduced because of absorption but there is a much greater proportion of back to forward scatter Any q values higher than 0 7 have not been found from the analysis (except those believed to be spurious) and it *seems a reasonable* supposition that q does not lie outside the limits 0 4 to 0 7 except possibly for very *soft radiations*

Assessment of p

The primary object is to establish a value for p in terms of the parameters of depth beam area and radiation quality Some information may be deduced from the formula $p = \dfrac{1+q\varphi}{1+\varphi}$ either directly or by differentiating with respect to the various parameters For very *small* areas for example, where φ tends to

the magnitude of the ratio was found to be almost constant at 1·06 and this figure when equated to Γ^{1-q} gave a q of 0·55, in good agreement with the computer figure for the same depth. A similar analysis for 20 cm depth confirmed that, there too, q was independent of area.

The method was extended to the gamma rays from caesium 137 and cobalt 60, 4 MV roentgen rays, and soft roentgen rays of 2 mm Al and 3 mm Al HVT. All except cobalt 60 radiation showed good constancy with respect to area in the ratio of the φ values, yielding, at 10 cm depth, q's of 0·62, 0·53 and 0·48 for caesium 137, 4 MV, and the soft radiations, respectively. The reason why cobalt 60 did not conform is not clear — possibly anomalies exist in the published values — but the evidence, taken as a whole, seemed to indicate that q is independent of, or at least insensitive to, area. A consequence of this finding is that in the computer analysis the q values for the respective areas could be averaged, with marked improvement in the results. Fig. 3 shows these values for comparison with those obtained from the ratio of the φ values. Summarising the evidence, it appears that q is insensitive to beam area, and that it lies between 0·4 and 0·7, with an average value of 0·55. Except for a narrow range of medium voltages, where it falls with depth, no discernible variation with depth or quality has emerged. It is therefore proposed to accept a q of 0·55 for all conditions, with the proviso that it may be greater than 0·7 for very soft qualities. The effect on depth dose estimation of a small error in q is discussed later.

Consequences of forward scatter

The circumstance that q is less than 1 derives from the fact that scatter radiation is predominantly forward. The zone from which scatter reaches a point P at depth is asymmetric, being elongated towards the focus. The scattering centres in this zone are therefore on an average nearer the focus than the point itself, and so the intensity of the primary photons which cause the scatter changes, on increasing focal distance from f_1 to f_2, by a factor which is *less* than Γ.

If we regard the zone as composed of N scattering centres, the nth at distance x_n below the surface producing a fraction a_n of the total scatter, then

$$\Gamma^q = \sum_{n=1}^{N} a_n \left(\frac{f_2}{f_2+x_n} \cdot \frac{f_1+x_n}{f_1}\right)^2$$

for a change in focal distance from f_1 to f_2.

We define a single point the 'equivalent' or 'effective' scattering centre at distance $\bar{x}$ from the surface, such that the R.H.S. $= \left(\frac{f_2}{f_2+\bar{x}} \cdot \frac{f_1+\bar{x}}{f_1}\right)^2$

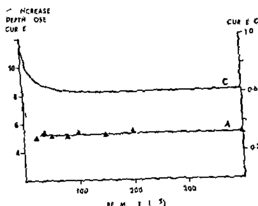


Fig 6 Curve (A) represents the percentage increase in depth dose with increase in focal distance from 40 to 50 cm at 1 0 mm Cu HVT and 10 cm depth Curve (C) represents p as a function of beam area at 2 0 mm Cu HVT and 20 cm depth ▲ indicate values from published data

effect of a change in focal distance a pure inverse square is therefore a good approximation at these energies especially where the change is small

(2) There is little variation of p over the whole range of soft and medium voltage qualities and the value of p for the diagnostic range (2 mm Al — 3 mm Al HVT) is the same as for 2 0 mm Cu HVT

Beam area Assuming that q does not change with beam area (A)

$$\frac{dp}{dA} = -\frac{1-q}{(1+\varphi)^2}\frac{d\varphi}{dA}$$

The formula enables an estimate to be made of the change of p with area and so is useful in the extrapolation of p to areas larger than 400 cm² which are common in diagnostic work For these φ is large and $\frac{d\varphi}{dA}$ is small and p changes very slowly with area (Fig 6) For diagnostic qualities at 10 cm depth p falls by only 0 02 for an area increase from 400 to 800 cm² and a figure of 0 62 is obtained for the larger area For 20 cm depth assuming p to be the same as for 2 0 mm Cu HVT the corresponding figure for 800 cm² is 0 58 Obviously, a p of 0 6 is suitable at all depths for large beam areas used in diagnostic radiology

The p v beam area curves are distinctive in the steep fall from unity for very small areas and the very slow decrease for areas greater than about 50 cm² The latter explains an interesting feature of published depth doses — that the fractional increase in depth dose on change of focal distance is found to be nearly constant over a wide range of beam areas Writing $F = (1 + p\alpha)$ the fractional change is $p\alpha$ and so varies as p As the formula above indicates the con

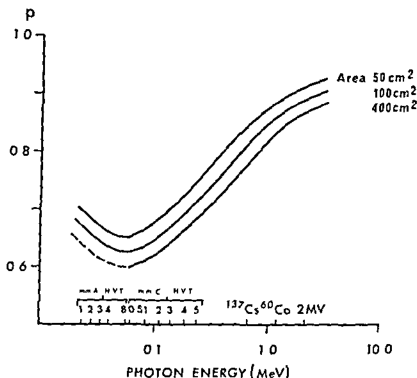


Fig. 5. Value of p at 10 cm depth as a function of the energy for beam areas 50, 100, 400 cm²

zero, p will approach unity. Because of the steep rise from the origin of the q' beam area graphs p at first falls rapidly from the value 1 at the origin and then more slowly. For large areas the rate of decrease is slight. Also, since $q<1$, it follows from the formula that $p>q$ and that for large q' values p approaches q.

Differentiating with respect to the parameter E (energy) we have

$$\frac{dp}{dE} = -\frac{1-q}{(1+q)^2}\frac{dq'}{dE} + \frac{q'}{(1+q)}\frac{dq}{dE}$$

with two similar equations for the parameters of depth and area.

Variation of p with energy, beam area and depth

Energy. When plotted against energy, q has a maximum about 8 mm HVT (Fig. 4), and, since q does not vary with energy over the medium voltage range, it follows from the differential equation that p must have a minimum value there. Features of the variation of p with energy are illustrated in Fig. 5, constructed for a depth of 10 cm using a q of 0.55. The following points are noteworthy.

(1) For high energies p reaches a value around 0.9. When estimating for the

Table 1

Percentage depth doses at 20 cm and 30 cm FSD derived from those published at 25 cm FSD by using the formula $p = \frac{1+q\varphi}{1+\varphi}$ *with* $q = 0\ 55$ *— The top rows are the published depth doses for comparison with the calculated values in the bottom rows — 4 mm Al HVT*

Area (cm²) FSD (cm)	0	5	10	15	25	50	100	200	300
20	4 9	5 7	6 7	7 5	8 6	10 6	12 7	14 5	—
	4 9	5 65	6 85	7 5	8 7	10 75	12 8	14 7	15 6
25	5 5	6 4	7 6	8 3	9 6	11 8	14 0	16 0	17 0
30	6 1	7 0	8 2	9 1	10 4	12 7	15 1	17 5	18 5
	6 0	6 8	8 2	8 9	10 3	12 6	14 9	17 0	18 1

The formula in practice

As an illustration of its effectiveness the formula has been used to calculate depth doses on change of focal distance for two qualities 4 mm Al HVT roentgen rays and cobalt 60 gamma rays and the results have been compared with published data

In Table 1 the depth doses have been calculated for 20 cm and 30 cm FSD *from those at 25 cm FSD* The top rows give published depth doses the bottom rows the calculated The agreement between the two is fairly good and in the two instances where the published data differ from the calculated by *more* than 0 2 it may be shown by deriving the q values that it is likely to be the published figures that are in error In this way the formula may be used as a means of detecting and smoothing errors

In Table 2 a *similar* analysis has been carried out for cobalt 60 gamma rays with a fairly large *change in SSD* — from 60 cm to 100 cm The difference between the calculated and *published* depth doses at 100 cm SSD is given in the error column also the q values *which* would have to be postulated to make the formula fit the published data *These* vary from 0 3 to 0 8 but the absence of any recognisable pattern either *with depth* or beam area and the fact that a q of 0 55 fits the data for the 15 cm square *field* very *well* suggests that the high values for the 10 cm square field and *the low* values for the 20 cm square field are due to errors in the published data

Accuracy of the formula Since q has been determined only approximately consideration must be given to the error *in* depth dose estimation caused by an error in q

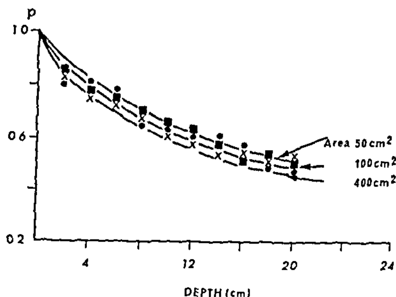


Fig. 7. Value of p as a function of depth for beam areas 50, 100, 400 cm² and 1.5 mm Cu HVT: comparison between individual values from published data and those from computer analysis. Computer results full curves. Individual values from published data: ● area 50 cm², ■ area 100 cm², × area 400 cm².

stant relation is most nearly approached for large φ values. Fig. 6 shows this for a HVT of 1.0 mm Cu and a depth of 10 cm, the increase when the focal distance changes from 40 to 50 cm being about 5% for beam areas 20 to 400 cm². The factor for zero area is Γ (in this case 1.082) and the graph curves steeply up to this value at the origin.

Depth. In view of the findings previous to this investigation that p lies between 1 and 0.5, it is of some interest to examine whether it may possibly fall below 0.5. Clearly, if at all, it will do so for a quality near its minimum and for large values of φ, i.e. large areas and depths. Since $q<p$, q must also fall below 0.5. Now the computer analysis for 1.5 mm Cu HVT gave $q = 0.4$ at 20 cm depth, and for this a φ of 5 or greater would make $p<0.5$. This value of φ at 20 cm depth is attained for a beam area of 70 cm², and it would therefore seem possible for p to fall below 0.5. Obviously the value of q is critical and until low values less than 0.5 are established, the question cannot be absolutely decided, but the relation between p and depth (Fig. 7), using the computer values of q, and on which are superposed the p values obtained from the published figures, produces strong evidence that P may fall below 0.5 for depths of 16 cm and greater. The figure is instructive in showing the spread in the p values calculated directly from the tables; it shows, too, that the formula fits the experimental data well.

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Area (cm²) / FSD (cm)	2	5	10	15	25	50	100	200	300
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	6 0	6 8	8 [illegible]	8 9	10 3	12 6	14 9	17 0	18 1

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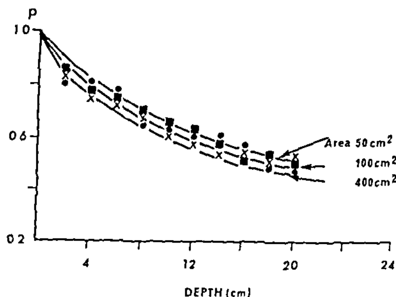


Fig 7 Value of p as a function of depth for beam areas 50 100 400 cm² and 1 5 mm Cu HVT comparison between individual values from published data and those from computer analysis Computer results full curves Individual values from published data ● area 50 cm² ■ area 100 cm² × area 400 cm²

stant relation is most nearly approached for large q values Fig 6 shows this for a HVT of 1 0 mm Cu and a depth of 10 cm, the increase when the focal distance changes from 10 to 50 cm being about 5 % for beam areas 20 to 400 cm² The factor for zero area is Γ (*in this case 1 082*) *and the graph curves steeply up* to this value at the origin

Depth In view of the findings previous to this investigation that p lies between 1 and 0 5 it is of some interest to examine whether it may possibly fall below 0 5 Clearly if at all, it will do so for a quality near its minimum and for large values of q i e large areas and depths Since $q<p$, q must also fall below 0 5 Now the computer analysis for 1 5 mm Cu HVT gave $q = 0\ 4$ at 20 cm depth, and for this a q of 5 or greater would make $p<0\ 5$ This value of q at 20 cm depth is attained for a beam area of 70 cm² and it would therefore seem possible for p to fall below 0 5 Obviously the value of q is critical and until low values less than 0 5 are established, the question cannot be absolutely decided, but the relation between p and depth (Fig 7), using the computer values of q, and on which are superposed the p values obtained from the published figures, produces strong evidence that P may fall below 0 5 for depths of 16 cm and greater *The figure is instructive in showing the spread in the p values* calculated directly from the tables, it shows, too, that the formula fits the experimental data well

error of 0.2 in q does not give rise to any gross discrepancy in depth dose calculation. Where φ is small, as for high energies, the error is very small indeed.

Conversely, the requirements for the experimental determination of q are more stringent for high energies. If it is desired to obtain q at such energies to within 0.1, the percentage depth dose at two FSD's must be measured with an accuracy better than the first decimal place, and this is difficult. With medium voltage a q difference of 0.1 may correspond to a change of 0.5 or greater in the percentage depth dose and should be detectable experimentally. No doubt the increased variance of q when qualities other than medium voltage are analysed is due in some measure to this.

A second source of error is that involved in the solution of the equation $\frac{F+F^q}{1+\varphi} = F^p$ by the use of the first term only in the binomial expansions of F^p and F^q. Considering also the second term in the expansions the solution becomes

$$p\,(1+\varphi) = (1+q\varphi) + \frac{a}{2}\,\frac{\varphi}{1+\varphi}\,(1-q)^2$$

giving for the fractional error in p,

$$\frac{a}{2}\,(1-q)^2\,\frac{\varphi}{(1+\varphi)\,(1+q\varphi)}$$

The function $\frac{\varphi}{(1+\varphi)\,(1+q\varphi)}$ may be shown to have a maximum when $\varphi = q^{-\frac{1}{2}}$ and the maximum fractional error then becomes

$$\frac{a}{2}\,(1-q)^2\,\frac{q^{-\frac{1}{2}}}{(1+q^{-\frac{1}{2}})\,(1+q^{\frac{1}{2}})}$$

Substituting $q = 0.55$, this is equal to $0.034\,a$. Even with an extreme value of a such as 0.25 the error in p is not more than 0.01.

Conclusions

1. The formula $p = \frac{1+q\varphi}{1+\varphi}$ determines F^p, the factor which converts one depth dose to another on change of focal distance, *in terms of* q, the parameter representing the variation of scattered radiation with focal distance.

2. The accuracy of published data has proved insufficient to yield precise q values, but the analysis has indicated that q is likely to lie between 0.4 and 0.7 for this data with an average of 0.55. Theoretical considerations of scatter

Table 2

Comparison between published percentage depth doses at 100 cm SSD with those calculated from the values at 60 cm SSD by the formula $p = \dfrac{1 + q\varphi}{1+\varphi}$ using $q=0.55$ — The error is the difference calculated minus published values — The values in the q column are those which, applied in the formula instead of 0.55 would make the error zero — Cobalt 60 gamma rays

Depth in cm	Field size 10 cm × 10 cm				Field size 15 cm × 15 cm				Field size 20 cm × 20 cm			
	Published	Calculated	Error	q	Published	Calculated	Error	q	Published	Calculated	Error	q
2	93.9	93.9	0	0.55	94.6	94.5	−0.1	0.6	94.7	94.75	+0.05	0.5
4	84.7	84.7	0	0.55	85.9	85.9	0	0.55	86.3	86.6	+0.3	0.4
6	75.5	75.25	−0.25	0.75	77.3	77.05	−0.15	0.7	78.1	78.3	+0.2	0.45
8	66.4	66.0	−0.4	0.8	68.7	68.6	−0.1	0.6	70.0	70.25	+0.25	0.4
10	57.8	57.6	−0.2	0.7	60.6	60.5	−0.1	0.6	62.3	62.75	+0.45	0.35
12	50.3	50.1	−0.2	0.7	53.4	53.3	−0.1	0.6	55.3	55.85	+0.55	0.35
14	43.9	43.6	−0.3	0.75	47.1	47.0	−0.1	0.55	49.1	49.7	+0.6	0.35
16	38.3	38.0	−0.3	0.75	41.5	41.5	0	0.55	43.5	44.2	+0.7	0.3
18	33.5	33.1	−0.4	0.75	36.7	36.6	−0.1	0.55	38.6	39.4	+0.8	0.3
20	29.3	28.8	−0.5	0.8	32.4	32.25	−0.15	0.6	34.4	35.0	+0.6	0.35

From $p = \dfrac{1+q\varphi}{1+\varphi}$ we have $\delta p = \dfrac{\varphi}{1+\varphi}\,\delta q$, and so the error varies with the magnitude of q

Writing $F^p = 1 + pa$, the fractional error introduced into the depth dose because of an error δp in p is $\dfrac{a\delta p}{1+pa}$ or $\dfrac{\varphi}{1+\varphi}\,\dfrac{a\delta q}{1+pa}$

Normally this is quite small for an error of 0.1 or 0.2 in q Its magnitude is perhaps best realised by calculating it for two conditions, in one of which q is small, in the other large

1 With 4 MV roentgen rays, 10 cm square field depth 10 cm, and FSD changed from 80 to 100 cm, $\varphi = 0.3$ Fractional error in depth dose corresponding to an error of 0.1 in q = 1 part in 1 000

2 With 1.5 mm Cu HVT roentgen rays, 10 cm square field depth 10 cm and FSD changed from 60 to 80 cm, $q = 2.6$ Fractional error in depth dose corresponding to an error of 0.1 in q = 5 parts in 1 000

The percentage depth dose in (2) is 37.8 at 80 cm FSD If q were in error by 0.2, the error introduced would be 0.4

Clearly, even in the worst cases where q is large a comparatively large

error of 0 2 in q does not give rise to any gross discrepancy in depth dose calculation Where φ is small as for high energies the error is very small indeed

Conversely the requirements for the experimental determination of q are more stringent for high energies If it is desired to obtain q at such energies to within 0 1 the percentage depth dose at two FSD s must be measured with an accuracy better than the first decimal place and this is difficult With medium voltage a q difference of 0 1 may correspond to a change of 0 5 or greater in the percentage depth dose and should be detectable experimentally No doubt the increased variance of q when qualities other than medium voltage are analysed is due in some measure to this

A second source of error is that involved in the solution of the equation $\frac{F+F^q}{1+\varphi} = F^p$ by the use of the first term only in the binomial expansions of F^p and F^q Considering also the second term in the expansions the solution becomes

$$p\ (1+\varphi)=(1+q\varphi)+\frac{a}{2}\ \frac{\varphi}{1+\varphi}\ (1-q)^2$$

giving for the fractional error in p

$$\frac{a}{2}\ (1-q)^2\frac{\varphi}{(1+\varphi)\ (1+q\varphi)}$$

The function $\frac{\varphi}{(1+\varphi)\ (1+q\varphi)}$ may be shown to have a maximum when $\varphi = q^-$ and the maximum fractional error then becomes

$$\frac{a}{2}\ (1-q)^2\ \frac{\varphi^-}{(1+q^-\ )\ (1+q\ )}$$

Substituting $q = 0\ 55$ this is equal to 0 034 a Even with an extreme value of a such as 0 25 the error in p is not more than 0 01

Conclusions

1 The formula $p-\frac{1+q\varphi}{1+\varphi}$ determines F^p the factor which converts one depth dose to another on change of focal distance in terms of q the parameter representing the variation of scattered radiation with focal distance

2 The accuracy of published data has proved insufficient to yield precise q values but the analysis has indicated that q is likely to lie between 0 4 and 0 7 for this data with an average of 0 55 Theoretical considerations of scatter

suggest that q may be greater than 0 7 for small areas at very soft qualities, but this lies outside the scope of the analysis

3 It is probable that q is independent of, or at least insensitive to, area, possibly to quality as well Depth variation is uncertain except for a small range of medium voltage qualities, where it falls with depth

4 The error in Γ^p resulting from a possible error introduced by the use of $q = 0$ 55 has been examined and found to be small, especially for high energies *Probably the greatest uncertainty in q exists in the very soft quality range* and it is here that its experimental determination might be most rewarding

5 The accuracy of the formula is such as to make it possible to publish depth doses for one FSD only instead of for two or more focus skin distances

6 Points of special interest are, first, the turning value in the p v quality graph, second, the shape of the p v beam area graph which confirms the observation that for large areas a change in focal distance produces a fractional increase in depth dose which is almost independent of area, and third the p v depth graph for 1 5 mm Cu HVT, which suggests that p may fall below 0 5

Acknowledgements

It is a pleasure to acknowledge the valuable help given by Mr H J A Scott during the earlier part of the work and that of Mr J W K Robertson in computer programming

SUMMARY

The manner in which roentgen depth dose depends on focal distance is described in terms of a *formula involving the parameter which represents the variation of scatter radiation with focal* distance Practical applications of the formula are given and some consequences of its application to published data discussed

ZUSAMMENFASSUNG

Die Abhangigkeit der Rontgentiefendosis vom Fokusabstand wird durch eine Formel beschrieben in der ein Parameter eingefuhrt wird womit die Variation der Streustrahlung mit dem Fokusabstand charakterisiert wird Anwendungsbeispiele dieser Formel werden gegeben und ihre Applikation auf publizierte Daten wird diskutiert

RESUMÉ

L auteur propose une formule dans laquelle intervient le paramètre qui represente la variation du rayonnement *diffusé en fonction de la distance focale pour montrer l effet de la* distance focale sur la dose en profondeur obtenue avec les rayons de roentgen Il donne des applications pratiques de cette formule et examine certaines conséquences de son application aux données *de la littérature*

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INTERSTITIAL IRRADIATION OF THE PITUITARY GLAND WITH A ^{90}Sr—^{90}Y APPLICATOR HAVING ADJUSTABLE ACTIVE LENGTH

by

N. E. Barring, A. Holmer, G. Notter and B. I. Rudén

The use of a ^{90}Sr applicator for pituitary irradiation offers important advantages compared with the implantation of ^{90}Y or ^{198}Au cylinders. The implantation technique is easier and more reliable with the ^{90}Sr applicator, and fractional or postoperative irradiations can be safely performed. The required radiation doses are lower with the ^{90}Sr applicator than with permanent implants because *of the much higher dose rate of the former.* Evaluation of dosimetric data, essential both for planning and application of interstitial irradiation, becomes more simple and accurate. The long half life of ^{90}Sr (28 y) makes it possible to use the applicator many years, which means lower costs per irradiation.

A ^{90}Sr applicator of this type was first developed by Mullan et coll. (1963), the clinical results from its use in neurosurgery being reported by Harper et coll. (1965).

Two identical ^{90}Sr applicators were constructed at *AB Atomenergi, Studsvik,* Sweden, in the spring of 1966 (Holmer et coll. 1967). Clinical results of the

Submitted for publication 21 October 1968.



Fig 1 Applicator knob and ^{90}Sr needle (1 mm outer diameter) with the movable outer tube the shutter (2 mm outer diameter) The length of the source not covered by the shutter is read on the millimeter scale Shutter position is adjusted with a screw mechanism on the applicator knob Total applicator length = 30 cm

interstitial irradiation of 22 patients were recently published by NOTTER et coll (1968) Histologic post mortem investigation of some pituitary glands indicated that the applicator when implanted centrally in each half of the hypophysis was too short (4 5 mm in length) to effect total destruction of the gland, considerable remnants of viable pituitary tissue remained in its anterior and posterior parts The implantation technique was therefore changed to two applications on both sides one in the anterior and the other in the posterior part of the gland Total hypophyseal destruction was thereafter achieved in all accurately implanted cases

To avoid time consuming double treatment a new applicator, with a maximum length of 14 mm and adjustable to varying sizes of the hypophysis was constructed The dose rate of the applicator was also increased to shorten the irradiation time as much as possible

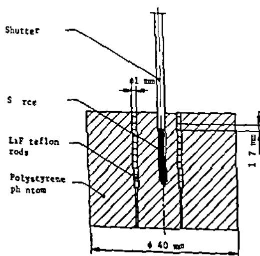


Fig 2 Experimental arrangement for measuring the dose distribution around the ^{90}Sr ^{90}Y source

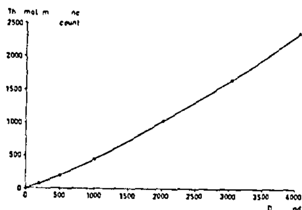


Fig. 3

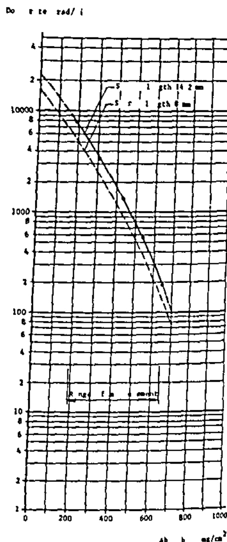


Fig. 4

Fig. 3. Calibration curve with measured thermoluminescence plotted against doses of ^{60}Co radiation received by the LiF teflon rods.

Fig. 4. Depth dose curves with dose rates measured at increasing distances from the surface of the ^{90}Sr needle along its minor axis.

Construction of the applicator. The ^{90}Sr source of the applicator was prepared by the technique described by HOLMER et coll. (1967). Strontium 90 was precipitated as $SrSO_4$ in a water-ethanol solution and after several washings with pure ethanol the precipitate was centrifuged down to the sealed tip of a hypodermic needle, 40 mm in length, 1.0 mm outer diameter and 0.72 mm inner diameter. The precipitate was dried by gentle heating and was then compressed into the tip by a rod that fitted exactly. The preparation procedure is reproducible so it was possible to obtain a $SrSO_4$ precipitate of the desired length of 14 mm containing 300 mCi ^{90}Sr. The needle was carefully decontaminated by washing in citric acid, EDTA and water, and was then fastened by thread and

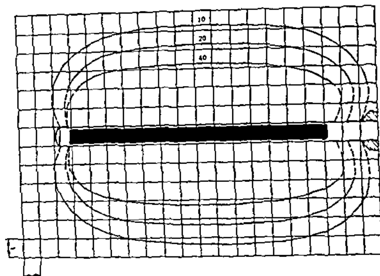


Fig 5 Isodose lines around the ^{90}Sr source The figures indicate the per centage dose delivered at 2 mm from the needle wall

glue to the applicator handle consisting of a stainless rod 1 5 mm in diameter A knob was sealed in place onto this handle (Fig 1) The knob has an internal thread forming a screw mechanism with an external thread on an outer stainless tube of 2 mm outer diameter concentric to the handle and needle The outer tube in the following called the shutter is at the applicator knob connected to a millimeter scale on which the length of the source not covered by the shutter can be read The readings may be made within 0 5 mm in the range 2 to 14 mm The shutter is 0 5 mm thick and absorbs about 93 % of the β radiation from the part of the source it is set to cover

Dosimetry

Method Dosimetric data for the ^{90}Sr-^{90}Y source of the applicator were measured by thermoluminescent dosimetry with lithium fluoride phosphors The dosimeters consisted of about 4 % LiF suspended in teflon (Bjarngard & Jones 1967) in the form of rods 1 mm in diameter by 1 7 mm in length

The experimental arrangement used for measuring depth dose and isodose contours around the applicator is presented in Fig 2 The ^{90}Sr applicator was placed in polystyrene (density 1 04 gcm^{-3}) in which were drilled 1 mm holes at different distances from the applicator The holes were filled with LiF teflon rods and the whole polystyrene phantom was placed in water during the meas-

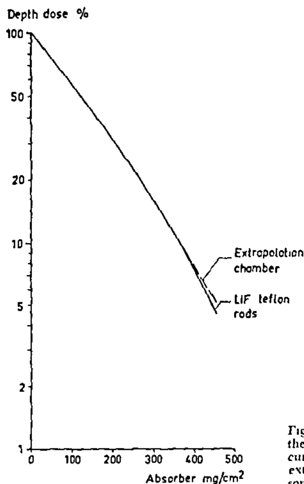
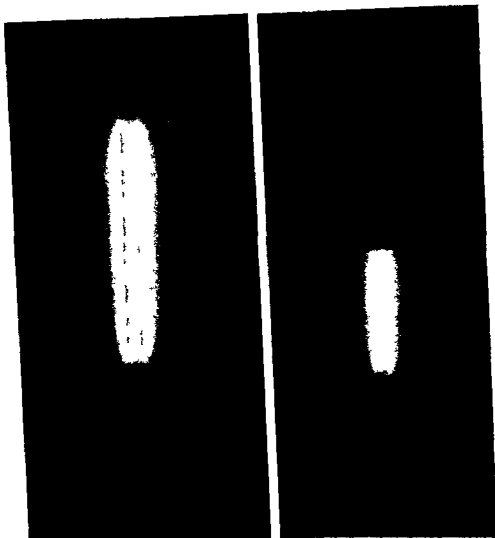


Fig. 6. Relative depth dose data normalized to the dose at the needle wall. The depth/dose curve obtained by SUPE & CUNNINGHAM with an extrapolation chamber is shown for comparison.

urements. Depending on their position, the LiF dosimeters received doses of between 25 and 4 000 rad. All LiF phosphors have some shallow traps that produce thermoluminescence peaks at room temperature immediately following irradiation; these decay in about one day. To avoid waiting for a 24 hour interval between exposure and read out, the emptying of the shallow traps was speeded up by placing the irradiated dosimeters in an oven at 80° C for 15 minutes. Thermoluminescence measurement could then be performed a short time after this treatment. A read out instrument (made by Controls for Radiation Incorporated, Mass. U. S. A.) was employed for all the thermoluminescence measurements.

Calibration. Cobalt 60 radiation was used for the calibration of the LiF teflon rods. The calculated mean energy of the Compton scattered electrons from the ^{60}Co gamma radiation is about 0.6 MeV, while the mean β energy of ^{90}Y is 0.9 MeV. Most of the ^{90}Sr β is absorbed by the needle wall, which is equivalent



F g 7 L ght from the ^{90}S so rce when immers d in water (Cerenkov effect) a) Shutter fully withdrawn b) Shutter in intermediate pos tion

to about 1 1 mm tissue Experiments by KASTNER et coll (1967) demonstrated that the thermoluminescent output per unit weight and per unit absorbed dose is the same for ^{90}Y as for ^{60}Co Radiation beams from the ^{60}Co source were measured with an ion chamber calibrated by NBS (HULTBERG et coll 1959) A number of LiF teflon rods were placed in a polystyrene phantom during the ^{60}Co exposures The measured LiF thermoluminescence was plotted against the dose (Fig 3) Each point of this calibration curve represents the mean value from five separate LiF teflon rods The average standard error is 4 %

Results and Discussion

The thermoluminescence signals measured from LiF dosimeters placed in the polystyrene phantom at different radial distances from the midpoint of the ^{90}Sr applicator were converted to doses by means of the calibration curve The values are shown in Fig 4 plotted against the absorber thickness counted from the surface of the applicator The solid curve in the figure was obtained with the shutter fully withdrawn (14 2 mm active length) and the dashed curve with the shutter partly screwed down (8 0 mm active length)

The isodose contours measured around the applicator are shown in Fig 5 The dose values are given as percentages of the dose at 2 mm from the surface of the applicator on its minor axis The dose rate measured at this reference point taken as 100 % was 7 200 rad/min Relative depth dose data normalized to the dose at the surface are given in Fig 6 as function of absorber thickness An effective half value depth of about 1 mm polystyrene can be read from this curve The results are in good agreement with measurements by RUDEN et coll (1968) and NOTTER et coll (1968) The depth dose curve obtained by SUPE & CUNNINGHAM (1963) from measurements on a ^{90}Sr source with an extrapolation chamber is included in Fig 6 for comparison The curve measured with LiF teflon rods falls off faster than that obtained with the extrapolation chamber A probable explanation of this difference is that a special energy dependence problem arises at low β energies a considerable dose gradient may exist within the dosimeter which can indicate only the average dose within its *volume*

Dose rates measured in different directions (the applicator was turned 90 degrees between each exposure) disclosed good cylindrical symmetry of the radiation field

SUMMARY

A ^{90}Sr applicator for interstitial irradiation of the pituitary gland is described The radiation source consisted of 300 mCi ^{90}Sr as strontium sulphate hermetically sealed into the end of a stainless steel needle Measurements of the dose distribution around the 90Sr 90Y source were made by thermoluminescent dosimetry with lithium fluoride phosphors

ZUSAMMENFASSUNG

Ein Applikator fur Implantationsbestrahlung der Hypophyse mittels Strontium 90 wird beschrieben Dieser besteht aus einer hermetisch verschlossenen Nadel aus rostfreiem Stahl, die an einem Ende mit 300 mCi von Strontium 90 in Sulphatform gefullt war Die Dosisverteilung in der Umgebung dieser 90Sr 90Y Strahlenquelle wurde mittels der Thermolumineszenz des Lithiumfluoridphosphors gemessen

RÉSUMÉ

Description d un applicateur de ^{90}Sr pour l irradiation interstitielle de l hypophyse La source des radiations est constituee par 300 mCi de ^{90}Sr sous forme de sulfate de strontium hermetiquement scelle à l extremite d une aiguille en acier inoxydable Les mesures de distribution de dose autour de la source de ^{90}Sr ^{90}Y ont été faites par dosimetrie de thermoluminescence avec scintillateur de fluorure de lithium

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EEG EFFECTS OF POSTOPERATIVE IRRADIATION TREATMENT OF BRAIN TUMOURS

by

C H HAKANSSON M LINDGREN and I A SULG

Irradiation treatment following operation for malignant cerebral tumours has been a routine procedure for more than three decades The present tendency towards the use of high energy irradiation introduces the danger of the normal brain tissues also being affected so that it is essential to obtain more information on the influence of ionizing irradiation on the brain Electroencephalography has therefore been used to study the cerebral state before during and after the course of treatment Experience from these examinations which have been routine for about 10 years indicates that the irradiation effects on the EEG are impressive but difficult to assess by the conventional EEG interpretation ANDERSEN et coll (1964) demonstrated that the rhythmic cortical activity is controlled by thalamic structures the aim of the study was therefore to determine whether ionizing irradiation absorbed in the thalamic region can induce changes in the EEG record

Material and Methods Only cases in which a tumour dose was delivered to the thalamic and hypothalamic structures were selected Six patients fulfilled this criterion

Ionizing radiation was delivered from a ^{60}Co source (diameter 20 mm)

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(Siemens gammatron I) through two temporal fields, 8 cm×9 cm, either with an equally bilaterally divided dose or with a maximum dose from only one side of the head The dose per day was about 200 rad delivered to the tumour, corresponding to 180 to 200 rad to the thalamic regions The optimal tumour dose was 5 500 to 6 000 rad over five weeks, while the corresponding dose to the thalamic region was 4 500 to 5 000 rad

Case reports

Case 1 Male age 72 operated for malignant meningeoma of the right temporal lobe Irradiation started six weeks after operation the absorbed dose in the thalamic region was calculated at 5 300 rad over 35 days

Case 2 Male age 59 operated for a clivus chordoma Irradiation started nine weeks after operation The thalamic dose was 5 500 rad over 38 days

Case 3 Female age 52 extirpation of a malignant glioma (glioblastoma multiforme) of the right parietal lobe Irradiation started six weeks after operation The thalamic dose was 4 800 rad over 33 days

Case 4 Female age 26 extirpation of a glioma (astrocytoma grade II) of the left parietal lobe Irradiation started four weeks after operation The thalamic dose was 4 800 rad over 26 days

Case 5 Male age 35 with astrocytoma growing into the corpus callosum Resection of the right frontal lobe Irradiation started eight months after operation The thalamic dose was 5 400 rad over 42 days

Case 6 Female age 46 operated for a glioma (astrocytoma grade II) of the left parietal lobe Irradiation started five months after operation The thalamic dose was 5 000 rad over 39 days

Electroencephalographic studies

During the first postoperative week the EEG, interpreted conventionally, is usually unstable but will generally stabilize and present some movement in line with the recovery of the patient About one month later the EEG will usually be more or less steady so that any changes appearing during this month may have been induced by the irradiation itself In the postoperative stage the EEG was checked once or twice before the treatment was initiated Halfway through the treatment another EEG control was performed, followed by a final control at the end of the irradiation

EEG frequency analyses were carried out on records from the four different regions shown in Figs 1 to 4 (a) irradiation field on the tumour side, (b) the parieto occipital region of the tumour side (c) the irradiation field of the contralateral side (d) the parieto occipital region of the contralateral side The

postcentral regions outside the irradiation zone (fields b and d) are the brain regions where the alpha rhythm or other EEG background activity is best observed

The EEG records were analysed according to conventional clinical principles and in addition a manual frequency analysis by the modified method of SULG (1967 1969) was performed All the EEG activity in the 1—20 cycles/second frequencies was measured with the resolution for successive frequency classes of 1 cycle/second

The activity time (accumulated period time of waves present) in every class was then plotted in seconds as a frequency spectrum polygon To obtain a single numerical parameter for this frequency profile the mean period frequency (ratio between all counted waves and the corresponding total activity time in seconds) was chosen as the *frequency index of the EEG*

$$\frac{\sum_{f=1}^{20} n_f}{\sum_{f=1}^{20} n_f \frac{\frac{1}{cf-0\ 5}+\frac{1}{cf+0\ 5}}{2}} = \text{mean period frequency } (\overline{F}_p)$$

1 – 20 = frequency classes in cycles/second, n_f = number of waves present in a frequency class cf = center frequency in correspondint frequency classes

The mean group spectra for regions a b c and d i e the mean values *corresponding* to all the six cases are presented in Figs 1 to 4 The profiles in Fig 1 are from the irradiated zone (a) on the tumour side A clear cut *increase in the* low frequencies and an activity decrease in the alpha range occurred during treat *ment* This retardation in the EEG is reflected also in the decreased EEG index The changes are even more marked in the spectral profiles from *region (b)* out side the irradiated zone (Fig 2) The EEG index decreased from 8 4 to 6 8 cycles second during irradiation (see Fig 5) The normal value for the EEG index is 9 9 ± 0 8 (S D) A low index signifies an EEG containing either more low frequencies or less activity in the alpha *range*

The mean frequency *indices* for the six patients before and after irradiation are given in Fig 6 the retardation in the EEG is most marked on the tumour side and the reduction in the EEG index is considerable even outside the irradi ated zone

The trend is roughly the same on the normal side as on the tumour side (Figs 3 and 4) The irradiation effects on *the cerebral* activity in the alpha (8 to 12 cycles second) and the slow (1 to 5 *cycles/second*) frequencies were compared and no significant change in the alpha rhythm during treatment whether meas-

(Siemens gammatron I) through two temporal fields, 8 cm×9 cm, either with an equally bilaterally divided dose or with a maximum dose from only one side of the head The dose per day was about 200 rad delivered to the tumour, corresponding to 180 to 200 rad to the thalamic regions The optimal tumour dose was 5 500 to 6 000 rad over five weeks, while the corresponding dose to the thalamic region was 4 500 to 5 000 rad

Case reports

Case 1 Male, age 72 operated for malignant meningeoma of the right temporal lobe Irradiation started six weeks after operation the absorbed dose in the thalamic region was calculated at 5 300 rad over 35 days

Case 2 Male age 59 operated for a clivus chordoma Irradiation started nine weeks after operation The thalamic dose was 5 500 rad over 38 days

Case 3 Female age 52 extirpation of a malignant glioma (glioblastoma multiforme) of the right parietal lobe Irradiation started six weeks after operation The thalamic dose was 4 800 rad over 33 days

Case 4 Female age 26 extirpation of a glioma (astrocytoma grade II) of the left parietal lobe Irradiation started four weeks after operation The thalamic dose was 4 800 rad over 26 days

Case 5 Male age 35 with astrocytoma growing into the corpus callosum Resection of the right frontal lobe Irradiation started eight months after operation The thalamic dose was 5 400 rad over 42 days

Case 6 Female age 46 operated for a glioma (astrocytoma grade II) of the left parietal lobe Irradiation started five months after operation The thalamic dose was 5 000 rad over 39 days

Electroencephalographic studies

During the first postoperative week the EEG, interpreted conventionally, is usually unstable but will generally stabilize and present some movement in line with the recovery of the patient About one month later the EEG will usually be more or less steady so that any changes appearing during this month may have been induced by the irradiation itself In the postoperative stage the EEG was checked once or twice before the treatment was initiated Halfway through the treatment another EEG control was performed, followed by a final control at the end of the irradiation

EEG frequency analyses were carried out on records from the four different regions shown in Figs 1 to 4 (a) irradiation field on the tumour side, (b) the parieto occipital region of the tumour side (c) *the irradiation field* of the contralateral side, (d) the parieto occipital region of the contralateral side The

postcentral regions outside the irradiation zone (fields b and d) are the brain regions where the alpha rhythm or other EEG background activity is best observed

The EEG records were analysed according to conventional clinical principles and in addition a manual frequency analysis by the modified method of SULG (1967 1969) was performed All the EEG activity in the 1—20 cycles/second frequencies was measured with the resolution for successive frequency classes of 1 cycle/second

The activity time (accumulated period time of waves present) in every class was then plotted in seconds as a frequency spectrum polygon To obtain a single numerical parameter for this frequency profile the mean period frequency (ratio between all counted waves and the corresponding total activity time in seconds) was chosen as the *frequency index of the EEG*

$$\frac{\sum_{f=1}^{20} n_f}{\sum_{f=1}^{20} n_f \frac{\frac{1}{cf-0.5}+\frac{1}{cf+0.5}}{2}} = \text{mean period frequency } (\bar{F}_p)$$

1 – 20 = frequency classes in cycles/second, n_f = number of waves present in a frequency class cf = center frequency in corresponding frequency classes

The mean group spectra for regions a b c and d i e the mean values corresponding to all the six cases are presented in Figs 1 to 4 The profiles in Fig 1 are from the irradiated zone (a) on the tumour side A clear cut increase in the low frequencies and an activity decrease in the alpha range occurred during treatment This retardation in the EEG is reflected also in the decreased EEG index The changes are even more marked in the spectral profiles from region (b) outside the irradiated zone (Fig 2) The EEG index decreased from 8 4 to 6 8 cycles second during irradiation (see Fig 5) The normal value for the EEG index is 9 9±0 8 (S D) A low index signifies an EEG containing either more low frequencies or less activity in the alpha range

The mean frequency indices for the six patients before and after irradiation are given in Fig 6 the retardation in the EEG is most marked on the tumour side and the reduction in the EEG index is considerable even outside the irradiated zone

The trend is roughly the same on the normal side as on the tumour side (Figs 3 and 4) The irradiation effects on the cerebral activity in the alpha (8 to 12 cycles second) and the slow (1 to 5 cycles/second) frequencies were compared and no significant change in the alpha rhythm during treatment whether meas-

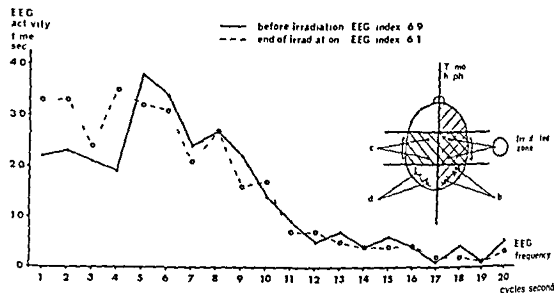


Fig 1 EEG frequency distribution as measured on the tumour side in the irradiated zone

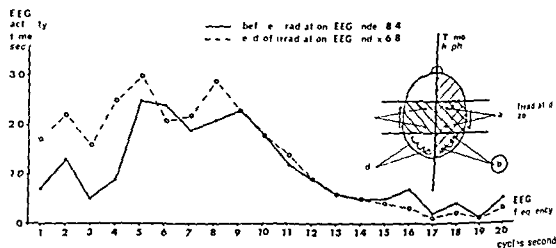
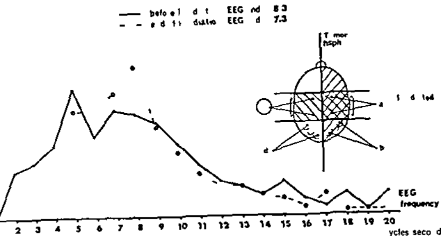
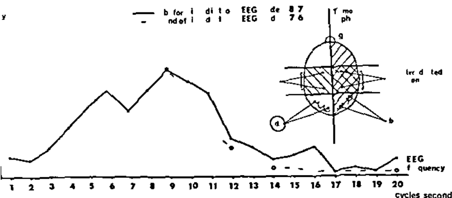


Fig 2 EEG frequency distribution as measured on the tumour side outside the irradiated field.

ured in the irradiation zone or in the tumour hemisphere (Fig 5) was observed The cerebral activity in the slow frequency range increased, however, especially in that part of the brain that was not influenced by direct irradiation (Fig 5, upper and middle diagrams) If the two hemispheres are compared (Fig 5, lowest diagram) the results are about the same an increase in the low frequency range but hardly any change in the alpha range The changes in the EEG index during irradiation of different cerebral regions are presented in Fig 6



EEG frequency distribution as measured on the non tumour side within the field of
ation



4 EEG frequency distribution as measured on the non tumour side w thin the field of
diation

Discussion

The dosage (in quantity) and fractionation time of the radiologic treatment
f cerebral tumours is empirically based on two fundamental observations

1 The early effect indicates the dosage quantity the patient can tolerate per
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eadache and somnolence probably due to an increase in the intracranial

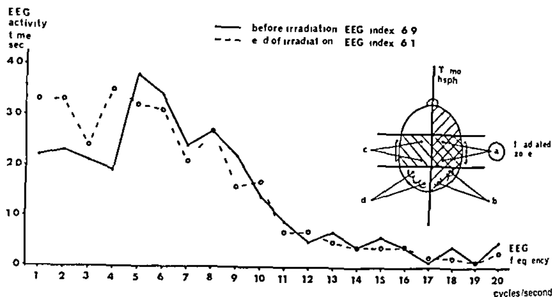


Fig 1 EEG frequency distribution as measured on the tumour side in the irradiated zone

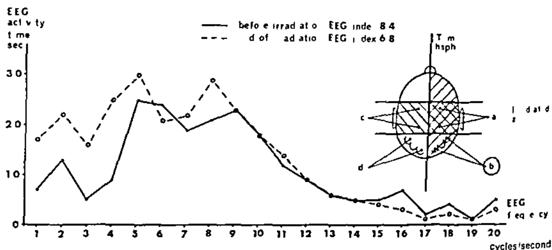


Fig 2 EEG frequency distribution as measured on the tumour side outside the irradiated field

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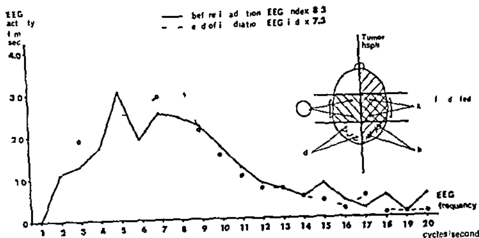


Fig 3 EEG frequency distribution as measured on the non tumour side within the field of irradiation

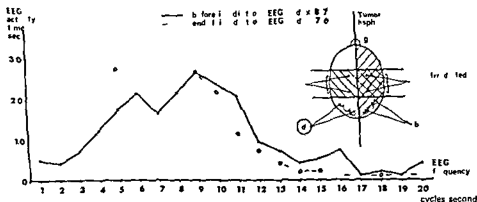


Fig 4 EEG frequency distribution as measured on the non tumour side within the field of irradiation

Discussion

The dosage (in quantity) and fractionation time of the radiologic treatment of cerebral tumours is empirically based on two fundamental observations

1 The early effect indicates the dosage quantity the patient can tolerate per day An excessive dosage quantity produces symptoms of malaise nausea, headache and somnolence probably due to an increase in the intracranial

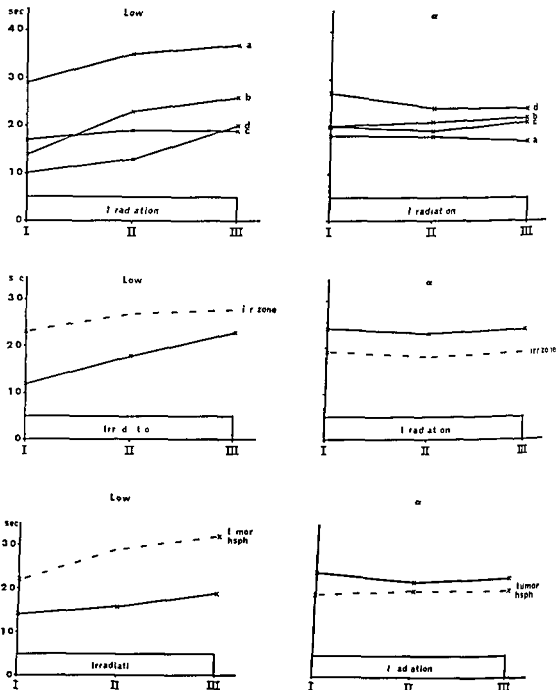


Fig 5 Mean activity time recorded for the low frequency range (1 to 5 cycles/second left row) and for the alpha frequency range (8 to 12 cycles/second right row) before irradiation (I) *after about 2 100 rad thalamic dose* (II) *and after about 4 500 rad thalamic dose* (III) The upper diagrams give the frequencies measured in regions a b c and d (cf figs 1 to 4) the middle diagrams the frequencies measured within the irradiated zone (a+c) and outside it (b+d) while the lowest diagrams give the frequencies measured on the tumour side and in the opposite hemisphere

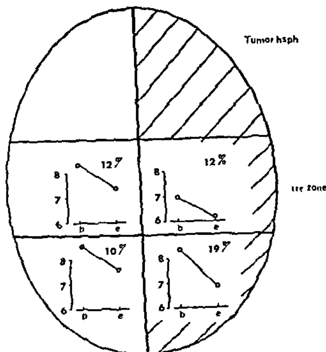


Fig 6 EEG indices obtained before (b) and at the end (e) of the irradiation

pressure arising from tissue oedema This was termed prereaction by BECLERE (1926) The fact that the doses in the present study did not produce increased pressure was shown by direct pressure measurements (HAKANSSON 1967)

2 The delayed effect reflects the reaction of the brain to the total irradiation dose measured by histologic calculation Overdoses produce radionecrosis BODEN (1950) reported 4 500 R/17 days for a region under 100 cm and 3 500 R/17 days for a region 100 cm as the maximum dose the adult brain can tolerate LINDGREN (1958) gave a slope in a fractionation diagram with the equation $y = 0\,26\,x + 3\,410$ as a tolerance limit for the adult brain These figures were based on four of his own cases and thirteen cases from the literature

In the radiologic treatment of cerebral tumours the optimal effect on the diseased tissues should be sought while at the same time irradiation damage to the normal parenchyma must be avoided Optimal results consequently always depend on a balanced adjustment The brain function must be the guiding principle

Few reports concerning the physiologic or psychologic responses of man to

ionizing radiation have to date appeared, most experience being based on animal experiments Only in recent years have studies been made in this field Thus, PAPP, HARASTA & PICHLER (1963) demonstrated the presence of changes in respiration after a dose of 2 rad to the diencephalon The responses however were not uniform, there was either an increase or a decrease in the frequency and volume of the respiration ROCCA & SANTI (1962) irradiated ten epileptic patients with eczema through two temporal fields (6 cm×8 cm) The roentgen rays also penetrated the hypophysis Six irradiations, each of 100 rad (i e 30 to 35 rad at the midline), were administered The amount of circulating eosinophils and the excretion of 17 ketosteroids and 11-oxysteroids were estimated during irradiation and fifteen days later The eosinophils dropped to their lowest value *after the second and the third irradiation, after which a slight increase occurred The excretion of 17-ketosteroids and 11 oxysteroids was minimal after the second and the third irradiation, and thereafter increased to exceed the initial level by* 200 per cent Not only the adrenal cortex reacted to the brain irradiation but the adrenal medulla as well, the same behaviour in the excretion of adrenalin as with the steroids occurred The authors compared the response with that obtained by electric stimulation of the hypothalamic region

The good systemic (hormone) response generally obtainable in the irradiation treatment of the diencephalon and hypophysis has led to indiscriminate irradiation treatment in numerous conditions RAMIOUL (1962) described 36 cases, including cases of ulcerative colitis chronic rheumatoid arthritis, asthma and a variety of malignancies which had been treated by irradiation of the diencephalon and hypophysis The irradiation was directed towards two temporal fields at 100 R per field three times a week until a total dose of 1 000 R per field was reached A number of positive results were recorded and some patients even showed steady improvement This modus operandi was stated quite *seriously to* be a 'method of choice

Even if the clinical effect is a liberation of hormones, or substances which influence the hormone balance, the effect of irradiation of an organic system is always deleterious to the structures, and the tissue is always impaired Furthermore, the irradiation dose that can be given must necessarily be limited There seems to be good reason therefore for a closer study of the irradiation effects on the human brain This has also been the reason for the quantitative routine study in our hospital of the electroencephalograms of patients who have been subjected to irradiation

In earlier studies the EEG was evaluated only qualitatively by conventional inspection of the tracings A quantitative transformation of the EEG frequency content was utilized in the present study It has been demonstrated by the same method in a large material that *a significant correlation exists* between the EEG

and the cerebral blood flow both in healthy controls and in patients with various cerebral disorders (INGVAR et coll 1965, SULG & INGVAR 1967 1968) Ionizing irradiation of the brain tissue has probably some effect on the cerebral metabolism and blood flow Retardation of the EEG in the waking state is usually a sign of depressed cerebral metabolism (OBRIST et coll 1963) Very slow activity (in delta frequencies) caused by brain tumours was first described by COBB (1945) and later by many other authors. Dysmetabolic cerebral disorders such as hepatoportal encephalopathy are another cause for the general retardation in the EEG (RORSMAN & SULG 1969, Fig 9) The present method of quantitative manual EEG evaluation has also been used to demonstrate the effect of tumours and cerebrovascular disorders on the EEG (SULG 1969 Fig 10)

In the present study a moderate general retardation was co existent with the low wave focus in the tumour region It was surprising to find that further retardation during the irradiation was more marked in the non irradiated regions than in the irradiated The effects in the tumour free hemisphere were most interesting because neither the neoplasm nor the operation trauma blurred the local conditions This region is therefore ideal for the study of pure irradiation effects on brain tissue The trend in the changes is however the same in all the regions analysed This general effect is probably due to the so-called remote effects as a result of the irradiation of diencephalic structures and especially the thalamus which is considered to generate and control the alpha rhythm in the human brain (ANDERSEN et coll 1964) These structures were irradiated in the present material with only about 2 100 rad (record II) but their neurophysiologic function as reflected in the EEG seems to reveal a detectable irradiation influence

The authors are not yet ready to make more definite conclusions about irradiation effects on different structures in the brain and further studies are proceeding in a larger clinical material What seems important is to draw attention to a change in the cerebral activity which is detectable at doses of half the maximum being given today in ordinary treatments

Acknowledgements

The authors wish to thank M Lipecki who assisted in the manual analysis of the EEG records The study was sponsored by grants from the B Kamprad Foundation

SUMMARY

Six patients were investigated to determine whether ionizing irradiation absorbed in the thalamic region could induce changes in the EEG record The preliminary results indicate that half the maximal doses being given today in ordinary treatments produce changes in the cerebral activity

ZUSAMMENFASSUNG

Es wurden Untersuchungen an sechs *Fällen vorgenommen um festzustellen* ob Bestrahlung des Thalamus Veranderungen im Elektroencephalogram hervorruft Vorlaufige Ergebnisse zeigen dass die Halfte der Maximaldose, die heutzutage bei der Behandlung ublich ist *genugt um Veranderungen der Hirntatigkeit* hervorzurufen

RÉSUMÉ

Les auteurs ont examiné six malades pour determiner si les radiations ionisantes absorbees dans la region thalamique peuvent causer des modifications de l electro-encephalogramme Les résultats preliminaires montrent que la moitie de la dose maximale administrée actuellement dans les traitements habituels produit des modifications de l activite cérebrale

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FROM THE DEPARTMENT OF RADIOLOGY YALE UNIVERSITY SCHOOL OF MEDICINE, NEW HAVEN CONNECTICUT, U S A

RADIATION TOLERANCE OF THE SKIN

by

CARL F VON ESSEN

The skin has a long history of detailed clinical observations on the damaging effects inflicted by ionizing radiation Recent knowledge of the cellular dynamics of the skin under normal conditions and in response to injury in addition to more precise methods of measuring radiation effects in cells and tissues permit new interpretations of many observed reactions These findings may indicate approaches to the reduction of radiation injury in this and other normal structures in order to improve the ability of radiation to selectively destroy malignant disease

Review of normal skin structure and cell kinetics

Cellular organization The skin is the largest organ of the body and functions as a *protective and* adaptive integument to the environment (65) It consists of the epidermis dermis or corium and subcutis The outer layer or epidermis has a thickness ranging from 0 1 to about 0 6 mm The *four layers of this* epidermis derive from randomly dividing basal cells in the germinal layer These cells differentiate progressively as they move through the prickle cell and granular cell layers and they eventually become part of the stratum corneum (Fig 1) The dermis serves as the base of nourishment for the epidermis It can vary in thickness

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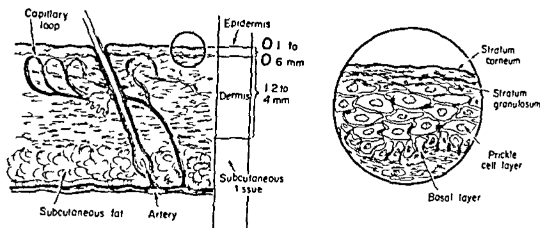


Fig. 1. Schematic illustration of the skin structure. The thickness of both epidermis and dermis varies in different body regions.

from 1.2 to 4 mm. The dermis supports specialized appendages such as the sweat glands, fat glands, and hair follicles and contains connective tissue elements of several types, blood vessels, muscle fibers and wandering mesenchymal cells. The dermis extends upward in papillae between rete ridges of the epidermis. These papillae contain vascular convolutions which provide nourishment for the avascular epidermis. The subcutaneous tissue contains predominantly fat cells and also a network of arteries, veins, and lymphatics which at intervals penetrate into the dermis.

Cell kinetics. The epidermis is a cell renewal system. The normal turnover time of the viable cell layer ranges from 13 to 18 days (30, 67), the passage time of cells through the entire thickness of the epidermis including the horny layer is between 22 and 31 days (5, 63).

The basal cells divide at random rates with an average cell cycle time of between 2 and 3 days in rats (67) and migrate towards the surface in a random manner (17). The hair follicles are also considered to be a cell renewal system. Basal cells of the follicle can divide as often as every 14 hours (62) and normally produce the hair keratin. Less is known about the cell kinetics of the resting dermis. Apparently little reproductive activity occurs among fibroblasts, endothelial cells and other fixed and wandering mesenchymal cells until a stimulus from injury occurs (25).

Cellular response of the skin to non-radiation injury

Within hours of injury, fibroblasts and histiocytes appear, presumably being transported through vascular channels from adjacent tissues (26). Adjacent basal

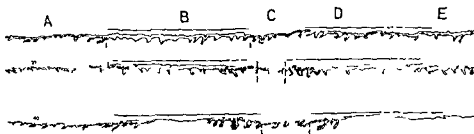


Fig 2 Camera lucida drawings of microautoradiographs of mouse epidermis showing cells labelled with tritiated thymidine at 5 days (upper tracing) at 6 days (middle tracing) and at 7 days (lower tracing) following a single dose of 2 700 R given to areas B D and E Areas A and C were shielded Increased labelling is noted at the radiation boundary and this with time progresses into the radiated zone (From DEVIK 1961)

epithelial cells proliferate and extend into the injured site by lateral extrusion (36 42) Mitotic activity increases in epithelial cells fibroblasts and multipotential histiocytic cells of the dermis (35) These latter cells are believed to differentiate into fibroblasts and endothelial cells and contribute in this way to the formation of capillaries in the granulation tissue (26) The general process of repair is characterized by intense migratory and mitotic activity of both dermal and epidermal cells *These processes subside during organization and contracture* of the wound and gradually a return to the resting state occurs The stimuli to this cellular activity are still not well understood but may include feedback mechanisms initiated by release of cellular components or chemical substances of injured cells and the loss of physical contact of continuity of the epithelium and dermis (3 18)

The area of the wound as well as depth is of vital importance to the subsequent degree of healing This area dependency was quantitatively characterized by DU NOUY (1916) over fifty years ago The area of injured skin was shown by him to be inversely correlated with the degree of subsequent healing The depth of the wound whether thermal as in 2nd and 3rd degree burns or traumatic also modifies the degree of healing and scar formation The integrity of the dermis is vital to the survival of overlying epithelium It will be seen that restitution of radiation injury of the skin follows similar patterns

Cellular response of the skin to radiation injury

Epidermis Acute doses of 1 000 to 4 000 rad produce a marked drop of mitotic activity within 12 hours in the radiated zone This is followed in a period of three to six days by hyperemia cell enlargement vacuolization nuclear

pyknosis and fragmentation (66) In serial observations on mouse skin receiving 2 700 R in a *single dose, and subsequently* exposed to tritiated thymidine, DEVIK (1961) noted a progressive centripetal increase of labelled cells extending from the radiation margin toward the center (Fig 2) In other experiments *the same investigator* demonstrated that central protection, even with thin wires of 0 05 mm, yielded zones of heavily labelled cells in the protected epithelium under the wires (21) *These cells spread over the radiated* surface at the speed of about 0 5 mm daily WITHERS (1967a) has also noted the marked protection afforded by quite small areas of radiation shielding with single doses up to 15 000 rad

This phenomenon of increased cellular activity at the radiation boundary has been noted *in other organisms (11, 64)* DEVIK *(1962) estimated cell cycle* times to be as short as 12 hours in a large proportion of epidermal cells at the radiation boundary within five days following a single dose of *2 700 R* The adjacent non irradiated cells had cell cycles over 24 hours while intermediate values were noted inside the radiated zone VAN DEN BRENK (1966) confirmed the findings of marked hyperplasia of the mouse epithelium at the margin and within the radiation zone two weeks following a single dose of 1 500 rad while *no regeneration within the radiated zone was noted when 3 000 rad were given*

Stimulation of the growth of resting hair follicles in mice has also been noted in the radiation boundary zone (3) This phenomenon was also noted after skin injuries produced by excision, chemicals and burns

WITHERS (1967a) has measured directly the radiation survival of mouse *epithelial cells in situ by the scoring of epithelial clones arising in* minute areas of irradiated skin shielded by various diameters of tiny spheres A surrounding area of skin was heavily irradiated *(3 000 R)* in order to prevent *repopulation* by peripheral cells The value for D_0 was 135 rad and a typical radiation cell survival curve was obtained The rate of re-epithelialization of the subsequent skin ulcers led to an estimate that approximately ten surviving epithelial cells were necessary in order to repopulate 1 cm^2 of denuded skin in ten days following *irradiation, a figure consistent* with DEVIK's measurement of the epithelialization rate of 0 5 mm per day The precise number of clonogenic cells per unit area of unirradiated epithelium is not known and *therefore other interesting* relationships i e D_q, the dose related to the shoulder of the survival curve and the extrapolation number, were not obtained

JOLLES (1950) has studied the factors contributing to the observed protection by adjacent shielding of skin during irradiation (as noted *in the clinical application* of grids or sieves) Neighboring radiated areas sustain increasing degrees of skin erythema reactions as the separating shielded skin area diminishes This *effect was attributed to a diffusable substance* released in ir

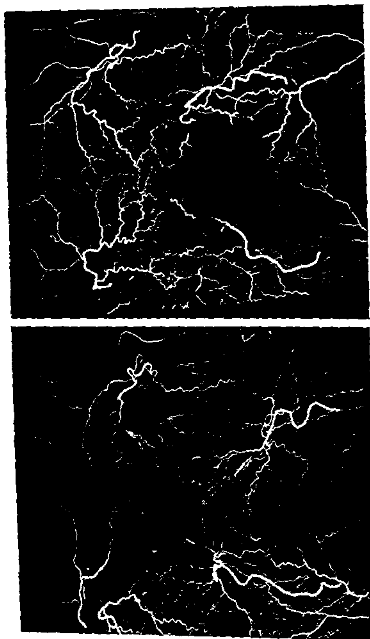


Fig. 3. Microarteriograms of irradiated rat skin. Avascular lesion produced 3 weeks following 4 000 R in 2 days to a 9 cm² area (upper view). Similar area showing neovasculature (lower view). (From ORDER, personal communication.)

pyknosis and fragmentation (66). In serial observations on mouse skin receiving 2700 R in a single dose, and subsequently exposed to tritiated thymidine, DEVIK (1961) noted a progressive centripetal increase of labelled cells extending from the radiation margin toward the center (Fig. 2). In other experiments the same investigator demonstrated that central protection, even with thin wires of 0.05 mm, yielded zones of heavily labelled cells in the protected epithelium under the wires (21). These cells spread over the radiated surface at the speed of about 0.5 mm daily. WITHERS (1967a) has also noted the marked protection afforded by quite small areas of radiation shielding with single doses up to 15000 rad.

This phenomenon of increased cellular activity at the radiation boundary has been noted in other organisms (11, 64). DEVIK (1962) estimated cell cycle times to be as short as 12 hours in a large proportion of epidermal cells at the radiation boundary within five days following a single dose of 2700 R. The adjacent non-irradiated cells had cell cycles over 24 hours while intermediate values were noted inside the radiated zone. VAN DEN BRENK (1966) confirmed the findings of marked hyperplasia of the mouse epithelium at the margin and within the radiation zone two weeks following a single dose of 1500 rad while no regeneration within the radiated zone was noted when 3000 rad were given.

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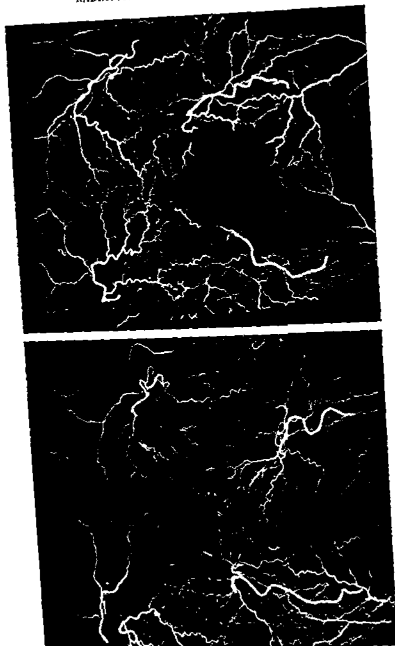


Fig. 3. Microarteriograms of irradiated rat skin. Avascular lesion produced 3 weeks following 4000 R in 2 days to a 9 cm^2 area (upper view). Similar area showing neovasculature (lower view). (From ORDER, personal communication.)

radiated tissues. Further investigation by perfusion of radiated and normal skin yielded a mitosis inhibiting perfusate with a survival time in situ of about 90 minutes following single doses of 1 200 to 2 000 R (JOLLES et coll. 1961). Chemical substances including histamine or histamine-like compounds have been reported to appear in the skin following local irradiation (54, 70). The skin response to these diffusable substances is not known. However, a generalized increase of mitotic activity throughout unirradiated rat epidermis occurring one week after local irradiation with 3 000 R has been reported (73). These findings suggest that diffusable substances may have a role in the cybernetics of response to radiation injury of the skin.

Dermis. In contrast to the epidermis, relatively few data are available concerning the kinetics of dermal response to injury. The survival of epidermal cells is dependent upon nutritional supply from blood vessels in the dermis. The capillary vasculature has been termed a conditional renewal system (62). Following radiation injury, capillary sprouting is generated by endothelial cells and multipotential mesenchymal cells up to spatial limits of 6 to 8 mm from the intact vessel (24). However, radiation doses of 2 000 to 5 000 R applied to mouse skin produce 'sterilized' blood vessels that are incapable of extensive regeneration (53). Vascularization following radiation of rat skin has been measured by means of micro-arteriography and compared to the findings with previous data on burn injury (59). Following 4 000 R in two daily doses, an avascular ulcer developed. Adequate vascularization occurred only in those ulcers that were not heavily infected by bacteria (Fig. 3). The role of bacterial infection in eventual ulcer healing was similar for both thermal and radiation wounds: where infection supervened, greater damage ensued, and revascularization did not occur (58).

DEVIK (1961) in his system noted the accumulation of a large number of labelled fibroblasts at the radiation boundary in juxtaposition to the labelled basal epithelial cells. Inward migration of labelled fibroblasts was similar to findings following surgical injury (43). Radiation induced ulceration has been reported to lead to fibroplasia in deep portions of the dermis raising the surviving dermal structures toward the skin surface and in this way permitting more effective reepithelialization and reconstruction of the defect (51).

It is thus likely that the dermis also responds in a dynamic fashion to cell loss from radiation injury by processes of cell proliferation and migration. The stroma of the sweat and sebaceous glands, the hair follicles and the blood vessels contain, however, relatively more fixed structures than epithelium and their cell kinetics of restitution are probably more limited in space and rate. It is probable, as remarked by ELLIS (1967), that the degree of dermal injury

is the fundamental lesion of skin damage since the epithelium is entirely dependent upon the functional integrity of the dermis

Applications to clinical tolerance

Observed reactions Radiation effects on the skin are related to radiation quality factors total dose dose periodicity size and depth of the irradiated area and to the overall time of irradiation The spectrum of early reactions ranges from threshold erythema to necrosis and these clinical skin reactions are generally classified as shown below

Degree of reaction	
1st	Threshold erythema a distinct reddening produced by vasodilatation
2nd	Dry desquamation loss of superficial layers of epidermis
3rd	Moist desquamation exudative reaction loss of basal layer of epidermis
4th	Necrosis irreversible ulceration dermal destruction

It is now believed that the magnitude of these early reactions is related to the degree and rate of epithelial cell death (36)

Severe irradiation injury of the dermis eventually results in more delayed effects such as fibrosis and endarteritis The visible manifestation may include atrophy with depression and loss of hair follicles and other skin appendages development of telangiectasia and the tendency of the skin to ulcerate A generally accepted maximum level of skin radiation tolerance has been the early 3rd degree of epidermitis (37) because severe late skin damage such as ulceration was considered unlikely at that level However as already outlined a host of factors are involved in tolerance ZATZ studied the late sequelae of a planned experiment in the radiation of normal skin of the thigh in human subjects 1958) Histologic studies were made at intervals from one to fourteen years following radiation The degree of severity of late skin changes was proportional to the dosage many severe late reactions however occurred below dose levels advocated clinically for maximum skin tolerance

STRANDQVIST (1944) derived time dose equations for skin reactions produced in the radiation therapy of skin cancer His equations do not consider the influence of field size the extent of skin destruction by tumor or the influence of treatment periodicity other than daily (approximately five treatments per week The curves obtained are generally called the Strandqvist plot and have been used extensively in numerous reports dealing with time dose relationships in the skin and have also been applied to reactions of other tissues Recent experimental studies including those by FOWLER and his associates (39 40 41) have indicated that reducing the periodicity (and therefore extending the interim

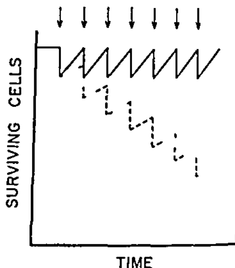


Fig 4 Differences in survival between two cell systems during fractionated radiation assuming that both have similar radiosensitivity but different rates of cell proliferation of surviving cells The upper curve can be considered a normal cell system and the lower a tumor cell system in order to illustrate the potential selectivity of small increments of radiation (represented by vertical arrows) in differentially sterilizing tumors (After OLIVER 1963)

between fractions) considerably alters the dose time relationship of the skin reaction from that predicted by the usual therapeutic schedule This increase of dosage per fraction increases the intensity of the skin reaction

Evidence that sufficiently low dose rates may lead to a net increase of cellular activity is seen in experiments on fractionated beta particle irradiation of rat skin (45) Fractions of 200 rad given at a periodicity of 48 hours resulted in enhanced local hair growth even after cumulated doses of 12 000 rad were reached However, doubling the fraction to 400 rad produced eventual epidermolysis Evidence that reducing the periodicity and increasing the fractional dose increases cell killing is seen in other cell renewal systems such as the gut (74) and marrow (13) These considerations were discussed by OLIVER (1963) in proposing a model to explain the effectiveness of fractionated radiation therapy in the selective destruction of malignant disease in situ if cell cycle times of normal tissues are considered to be shorter than those of tumors then an appropriate periodic fraction of radiation will selectively depopulate the tumor while permitting the normal tissue to repopulate to its original level between each fraction (Fig 4) This model assumes that no differences exist in radiation sensitivity between normal and malignant cells This assumption appears to be reasonable judging from the numerous reports on radiation survival curves of oxygenated normal and malignant cells in vivo and in vitro However, the cell kinetics of many normal cell populations, for example in stromal structures such as the dermis, may be considerably slower than those of some tumors Additional mechanisms should therefore be considered VAN DEN BRENK (1966) and others (12, 32) have suggested that in the skin and other radiated tissues normal cell repopulation occurs during fractionated radia

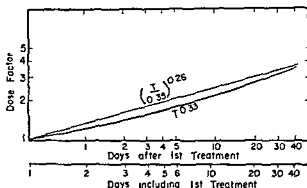


Fig 5 Comparison of two time dose isoeffect equations for skin reactions as drawn upon the Strandqvist plot (the time of initial treatment is considered equivalent to 0 35 days) These slopes are similar and for practical convenience may be considered together under the cube root rule where the initial treatment time is equal to 1 day as suggested by COHEN 1966

therapy by means of enhancement of reproductive activity and by centrip- migration of unirradiated specialized or multipotential cells following the ulus provided by the initial and continued radiation injury This tissue onse to injury may be another vital component of a *differential radiation* iage on two cell systems normal and malignant the former having the urces of surrounding related unirradiated cells the latter being without such ces of restitution It is evident that the dose rate in such a model is critical high a rate will destroy available repopulation elements too low a rate may progressively destroy *tumor cells*

WITHERS (1967b) measured recovery and repopulation of epithelium in ir iated mouse skin while eliminating peripheral potentially *repopulating* ele its by a heavily irradiated zone around the test sites The value $(D_2—D_1$ 24 irs) indicates the split dose difference between the sum of two doses D and single *fraction dose* D_1 when the two doses are separated by 24 hours When single fraction ranged from 385 to 1 050 rad the $(D—D^1)$ value was)—375 rad However for single initial *fraction* of 190 rad the $(D_2—D_1)$ ue was 290 rad which suggests an excess recovery equal to the effect of 100 l WITHERS considered the most likely explanation of this to be repopulation by ans of an enhanced doubling time of surviving epithelial cells It is interesting compare this data in mouse skin to the commonly applied clinical daily radia n fraction of 200—250 rad

Reduction of the periodicity of fractionated radiation diminishes skin tolerance

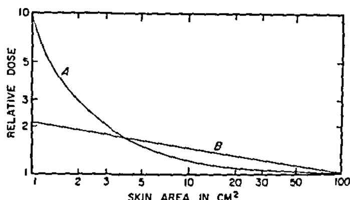


FIG. 6. Comparison of the slopes of two area dose isoeffect equations for skin tolerance. Curve A proposed by JOVET & HOHL has the equation $D=10\,k$ and curve B is $D=kA^{0.1}$ derived by various authors. The discrepancy is most marked for small areas. JOVET & HOHL's data refer to the isoeffect for healing of acute reactions (epidermal tolerance) in contrast to the other data which is based predominantly upon the isoeffect for late skin changes, i.e. dermal tolerance.

both in clinical radiation therapy (72) and in experimental animals (38). Attention was drawn to the proximal portions of the overall time scale on STRANDQVIST's skin tolerance graph by NIAS (1963) who found that the reactions of human skin irradiated in four daily fractions exceeded those predicted by that portion of the slope of the Strandqvist plot. FOWLER & STERN (1963) have also noted clinically documented departures from those predicted by the original Strandqvist plot in this portion of the time dose function. These findings suggest that large fractions may have a greater damaging effect on normal skin than was previously estimated.

The general concensus among recent clinical investigators (14, 28, 29, 31, 78) is that the isoeffect slope of the time dose relationship for both acute and late skin reactions is steeper than that obtained by STRANDQVIST and is most conveniently described by the cube root rule which has practical value because of the simplicity of calculation but is applicable only with the usual daily fractionation (five treatments per week). The equation reached by some authors (31, 78) using the Strandqvist plot

$$D=k\left(\frac{T}{0.35}\right)^{0\ \ 6}$$

is reasonably equivalent to the cube root function of COHEN (1951) and others $D=k\,T^{0.33}$ where the logarithm of time in days begins with 1 for the initial treatment (Fig. 5). ELLIS (1967) has introduced methods of calculating the time dose relationships with other fractionation periodicities.

Volume factor The maximum tolerance dose for normal tissues is inversely related to the volume irradiated Clinical data from ELLIS (1942) JOLLES & MITCHELL (1947), JOLLES & HOHL (1955) PATERSON (1963) VON ESSEN (1960) and others indicate that this relationship for the skin can be expressed in terms of area of irradiated skin because the depth of the skin is relatively constant provided the radiation homogeneity is fairly uniform throughout this depth Expressing these data in the form of an equation $D=kA$ where D is the dose to produce a given skin reaction with a radiation skin area of 1 cm² and k is a constant The exponent n refers to the change of skin tolerance with area Values for n range from — 0 165 for much skin tolerance data summarized by COHEN (1966) — 0 16 by VON ESSEN (1964) to — 0 12 by ALLEN & LREED (1966) for superficial quality roentgen rays JOLLES & HOHL s data (1955) differ significantly below approximately 3 cm where much higher dose levels were obtained for skin tolerance for short term observation than by other investigators (Fig 6) Their skin tolerance study involved planned radiation of the normal skin of patients with lung carcinoma at a fixed fractionation schedule while most other investigators studied the late reactions of skin already infiltrated by malignant tumors with varying fractionation schedules From clinical experience with the fractionated treatment of small skin carcinomas however it is inconceivable to consider that the maximum skin tolerance dose is as high as 50 000 R in 18 days for 1 cm fields or 15 000 R for 2 cm² fields as proposed by JOLLES & HOHL Their data should be considered as applicable for intact skin and for acute reactions only

As was previously suggested in the review of time dose data (56) a systematic error may be present in the retrospective interpretation of volume or area dose data small radiation fields are more often used with short fractionation schedules in comparison to large areas generally treated with long fractionation schedules The tolerance of small areas of intact skin therefore may in fact be higher than generally believed and the function relating tolerance to area may have a steeper lope

The consensus of the area dose relationship from the present available data however suggests that the function having greatest applicability to skin tolerance under conditions of clinical radiation therapy is $D=k_1 A^{0\,15}$ which is equivalent to $D=k\ L^{0\,3}$ where L is the diameter of the irradiated area This can be expressed in a practical sense as "the dose required to produce a given skin reaction is inversely proportional to the cube root of the diameter of the irradiated field (15)

Radiation quality The greater use of higher energy (or megavoltage) roentgen radiation and gamma radiation ...

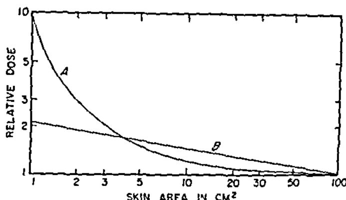


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The consensus of the area dose relationship from the present available data however suggests that the function having greatest applicability to skin tolerance under conditions of clinical radiation therapy is $D = k_1 A^{-0.16}$ which is equivalent to $D = k_2 L^{-1/3}$ where L is the diameter of the irradiated area This can be expressed in a practical sense as the dose required to produce a given skin reaction is inversely proportional to the cube root of the diameter of the irradiated field (15)

Radiation quality The greater use of higher energy (or megavoltage) roentgen radiation and gamma radiation from ^{60}Co in the past decade has tended to

reduce the significance of the skin as a limiting factor in radical radiation therapy of underlying tumors The so-called skin sparing effect of higher energies of radiation is related to the electron build up at depths under the skin surface varying from a few millimeters to several centimeters depending on the type of radiation This effect is obviated, sometimes deliberately, by reduction of the beam angle incident to the skin surface, the addition of bolus material, or the use of directly opposing fields Late skin damage has been frequently described following megavoltage or gamma radiation (50) The patterns of injury differ somewhat from that following radiation with lower energies subcutaneous damage including fat necrosis and severe subcutaneous scarring predominates These changes are generally accompanied by visible changes of the epithelium and dermis such as atrophy and pigmentation changes Ulceration is uncommon The use of megavoltage radiation, therefore, does not eliminate the limiting factor of maximum skin tolerance With proper treatment planning including the avoidance of single or directly opposing beams in high dose fields, as well as the judicious use of bolus only when skin dosage must be increased, and caution in treating intertriginous areas, the risk of late skin damage can be greatly reduced

Other factors influencing radiation tolerance

Oxygen It is now established that skin radiation tolerance is reduced by high pressure oxygen breathing and is enhanced by local hypoxia (4, 9, 10, 19, 60) The oxygen enhancement ratio (O E R) measured by the ratio of skin reactions (9, 69) or clonal regrowth of epithelial cells (77) between air breathing and high pressure oxygen breathing during radiation is about 1 2 A considerable proportion of skin cells appears to be well oxygenated as shown by the ratio of 2 6 found for cell survival in mouse skin between radiation effects *during* air breathing and extremity clamping or skin compression The fractional size of radiation dosage altered this ratio the O E R increased with single roentgen doses above about 750 rad (9) and with neutron radiation above 1 000 rad (20) These changes are attributed to the increasing importance of vascular damage at high doses and the greater RBE of neutrons at higher doses for the hypoxic proportion of skin cells

Using the end point of the acute skin reaction following irradiation of mouse legs during high pressure oxygen breathing with either 1 or 10 daily fractional doses, Suit & Howard (1967) found no change in the O E R However, under hypoxic conditions the reduction ratio of hypoxia air changed from 0 87 with one fraction to 0 68 when ten daily fractions were administered In planning optimal conditions of radiotherapy with high pressure oxygen breathing local

anoxia or with neutron radiation it may be as important to maintain the fractional dose below that level which begins to reduce the differential effect between tumor and normal tissues as it is in conventional radiation therapy

Other effects Skin cooling during radiation (52) and infra red or other sources of local heat have been reported to influence skin reactions, possibly on the basis of the oxygen effects Numerous substances applied topically or systemically have been claimed to affect radiation sensitivity of the skin Chloroquine (6) and steroid ointments (44) have been used to reduce the degree of the acute reaction but did not yield any long term improvements (7)

Chemotherapeutic agents are known to enhance the local reaction to radiation, particularly when the radiation treatment is followed by chemotherapy (1 33 34) This is presumably caused by interference with restitution kinetics

Carcinogenesis

Late malignant changes of irradiated skin have been reported for over 60 years TRAENKLE (1963) concludes that malignant change in the skin following therapeutic radiation for malignant disease is an uncommon event occurring almost only in the cases where visible severe radiation damage has been present for five years to several decades At present there is no indication that any particular set of treatment factors in therapeutically applied radiation given within the usual maximum treatment span of two months appear related to subsequent malignant changes provided that gross overdosage is avoided

Conclusions

The skin is a complex and dynamic structure responding to many types of injury in attempts at repair by means of increased rates of cellular proliferation and migration These cellular activities are limited in space and time thus rate and volume as well as degree of administration of injury determines the ability of the skin to heal Therapeutic irradiation is administered in an attempt to selectively destroy malignant cells and yet preserve enough normal tissue structure and function to be compatible with reasonably and productive life of the patient The selection of treatment factors including radiation type and energy dose volume periodicity and total treatment time should be chosen to produce an optimal difference between total tumor destruction and normal tissue damage The data presented indicate that epidermal and dermal repair is stimulated as a result of radiation injury to these tissues The usual way of treatment by giving the radiation doses in fractions rather than in a single treatment permit some

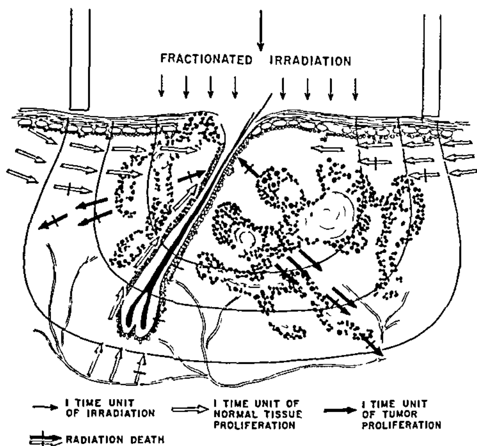


Fig 7 Schematic cross section of skin with tumor in situ demonstrating how by means of repopulation during fractionated radiation therapy normal tissue integrity can be preserved as tumor is destroyed The arrows depict time units of radiation repopulation or cell death Assuming that similar cell proliferation kinetics and radiation survival kinetics exist in normal and tumor cells this model suggests that differential survival of normal cells can be achieved during fractionated radiation of circumscribed areas.

intracellular recovery (in the radiobiological sense) and restitution (in terms of cell kinetics) Both these processes are likely to operate for cells surviving within the radiation zone while restitution by means of increased cellular proliferation and cell migration apply for surrounding unirradiated cells This dynamic repair during continued periodic or protracted radiation cannot endure indefinitely because an increasing number of slowly dividing or migrating cells, including those populating specialized structures will be killed and the stroma supplying necessary nutritional and structural support to the more rapidly dividing cells

will fail to survive. Therefore, minimal as well as maximal limits may exist for the total radiation period. The limitations on the rate and distance of migration of repopulating elements results in a diminishing tolerance with increasing volume (or area in the case of the skin). It is not known whether tumor cells in situ respond similarly to sublethal radiation doses by increasing their rate of proliferation. Even if this occurs, a model is proposed to demonstrate that a fundamental difference exists between normal tissue and tumor response which may be enhanced by protraction of radiation dosage: cells in surrounding unirradiated or marginally irradiated areas increase their rate of proliferation and migrate into the radiation zone, thus serving to preserve the integrity of the normal tissue stroma around and within the tumor (Fig. 7).

A general equation for skin tolerance can be derived from the separate equations previously discussed for time dose and area dose relationships:

since $D=k\ T^{0.33}$ and also $D=k\ L^{-0.3}$ then $D=k\sqrt[3]{\frac{T}{L}}$

where D is the cumulative dose of daily treatment in rad to produce a given reaction, T is the overall time in days including the first treatment, L is the equivalent diameter in cm of the radiation field and k is the proportionality factor referring to the dose given in a single treatment to a field of 1 cm diameter. The factor k for maximum skin tolerance appears to be in the range 2 700—3 100 rad.

The skin exhibits an increased radiation sensitivity when subjected to high pressure oxygen or some cancerocidal agents, indicating that continued caution should be used when embarking on programs of radiation therapy combined with these agents. Increasing the dose per fraction is associated with rapidly increasing skin damage even when the total dose overall time relationship is constant. There has been no good evidence so far to justify marked departures from the conventional fractionation programs, although the split dose modification may have validity.

The appearance of subcutaneous injury with the application of supervoltage radiation therapy emphasizes the vulnerability of vascular supply to the skin. Careful *planning of radiation distribution is* of continued importance since the skin sparing effect of high energy radiation is applicable only to the superficial layers of the skin; deep vascular and connective tissue injury may result in overlying skin damage.

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The author is indebted to H. S. Reinhold of the Department of Radiology and I. M. Braverman of the Department of Dermatology, Yale School of Medicine, for critical comment and suggestions.

SUMMARY

Dynamic processes of cellular recovery, proliferation and migration operate in response to radiation injury of the skin The accelerated proliferation rates of surviving epidermal and dermal cells in addition to migration of unirradiated cells into the radiated area may be of importance in differentiating restitution in tumors from normal skin Small increments of dose and limited areas of exposure favor normal skin repair processes The skin is moderately radiosensitized by high pressure oxygen and more markedly protected by anoxia Supervoltage radiation may damage skin by subcutaneous overdosage Isoeffect equations for time and area are probably over simplified but useful at the level of present knowledge within the general time periods of radiation therapy They can be restated thus the dose required to produce a given skin reaction varies with the cube root of the overall time of exposure expressed in days and inversely with the cube root of the diameter of the irradiated field

ZUSAMMENFASSUNG

Dynamische Prozesse von Zellerholung Zellproliferation und Zellwanderung sind als Antwort auf eine Strahlenschädigung der Haut wirksam Die beschleunigte Proliferation uberlebender epidermaler und dermaler Zellen mogen neben der Wanderung von unbestrahlten Zellen in das bestrahlte Gebiet bedeutungsvoll fur Unterschiede der Wiederherstellung in Tumoren und normaler Haut sein Eine langsame Dosissteigerung und die Bestrahlung begrenzter Felder begünstigen die Wiederherstellungsprozesse der normalen Haut Die Haut wird durch hohen Sauerstoffdruck massig strahlensensibilisiert und mehr markant durch Anoxie geschutzt Supervolt Bestrahlung mag die Haut durch subcutane Überdosierung schadigen Iso Effekt Gleichungen fur Zeit und Feldgrosse sind wahrscheinlich uber vereinfacht aber anwendbar vom Standpunkt unserer gegenwartigen Kenntnis innerhalb der allgemeinen Zeitperioden der Strahlentherapie Sie lassen sich folgendermassen ausdrucken Die Dosis eine gegebene Hautreaktion zu erzeugen verandert sich mit der Kubikwurzel der gesamten in Tagen ausgedruckten Bestrahlungszeit und ist umgekehrt proportional zur Kubikwurzel des Diameters des bestrahlten Feldes

RESUMÉ

L auteur a etudie les processus dynamiques de la restauration de la proliferation et de la migration cellulaire a la suite des radio lesions de la peau Le taux accélére de proliferation des cellules epidermiques et dermiques survivantes et la migration des cellules non irradiees vers l aire irradiee peuvent etre des facteurs importants pour distinguer la peau normale de la restauration dans les cas de tumeurs Une petite augmentation de la dose et une limitation des aires irradiees facilitent les processus normaux de restauration de la peau La peau est moderement radio sensibilisee par l oxygene sous forte pression et est protegee de façon plus marquee par l anoxie Les radiations de haute energie peuvent endommager la peau par un surdosage sous cutane Les equations d iso effet en fonction du temps et de la surface sont probablement trop simplifiees mais elles ont utiles compte tenu du niveau actuel de nos connaissances, pendant la duree generalement utilisee pour le traitement par les radiations On peut les resumer ainsi la dose necessaire pour produire une reaction cutanee donnee varie comme la racine cubique de la duree totale d irradiation exprimée en jour et e t inversement proportionnelle a la racine cubique du diametre du champ irradie

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DOSE RATES AND FIELD HOMOGENEITY OF SIEMENS 42 MeV BETATRON

by

JURGEN RASSOW

The dose rates of particle accelerators such as the betatron vary within wide limits by a number of parameters like cathode heating injection timing and capturing voltage and these must always be re adjusted for the purpose of obtaining an optimum dose rate For this reason the dose rate of particle accelerators has generally been considered of less importance if only high enough to allow short treatment times

With growing energy the bremsstrahlung reaches a maximum in the for ward direction in a similar manner the electron radiation becomes inhomo geneous The latter is emitted mainly in the nominal orbit plane and must be scattered by the use of say lead foils It would be easy to homogenize all field sizes by means of fixed homogenizers for all energies in the case of electrons and for the maximum energy in the case of bremsstrahlung The resulting insufficient dose rate necessitates a number of homogenizing filters to obtain optimum dose rate for all treatment conditions

This behaviour of the dose rate constitutes a decisive criterion for the assess ment of a betatron In spite of this manufacturers usually limit themselves to

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Table 1

Field size and useful field angle

Field width (FSD 100 cm) times	4	6	8	10	12	15	16.7	cm
Field width (FSD 120 cm) times	4.8	7.2	9.6	12	14.4	18	20	cm
Angles of useful field	2.3	3.5	4.6	5.7	6.9	8.6	9.6	degrees
Angles of useful field	0.04	0.06	0.08	0.10	0.12	0.15	0.167	radians

giving rather vague details, either as guaranteed minimum values, or in some other form, this is because of the difficulty of carrying out realistic and reproducible measurements of the dose rate, especially with varying test parameters. Such minimum values furnish only unsatisfactory information about the true obtainable values.

The data provided for users are extremely scanty and vary widely because the filters used for various field sizes and energies may differ in design and application to cover the effect of basic factors.

The present investigation was intended to reveal empirically the physically interesting laws and to facilitate an understanding of the quantitative effects and the application of various homogenizers and scattering foils as well as of dose rates obtainable for all therapeutic objectives.

1. Normalization and measuring conditions. All measurements of the dose or dose rate were performed with the standard chamber of the PTW Duplex dosimeter or the tube chamber of Philips dosimeter and invariably refer to the depth of the dose maximum in a polystyrol phantom of 25 cm × 25 cm × 25 cm. All exposures were converted into absorbed doses with those rd/R factors that prevail at the effective chamber site.

In order to become independent of the focus skin distances (FSD), the field dimensions are always indicated in useful field angles a which are defined as

$$a = \frac{\text{useful field width in the focus skin distance}}{\text{focus skin distance}}$$

A field width of 10 cm at 100 cm FSD results in an angle $a = 0.1$. The simple geometric relationship existing between a, measured in radians and in degrees, and the field widths at 100 and 120 cm FSD can be gathered from Table 1.

Straight forward normalization eliminates the long time dose rate fluctuations, the alternating determination of measurement and reference values excluding the short time values.

"Normalized dose rate" means the relationship that exists between the dose rate of the measured radiation and the dose rate of bremsstrahlung at maxi

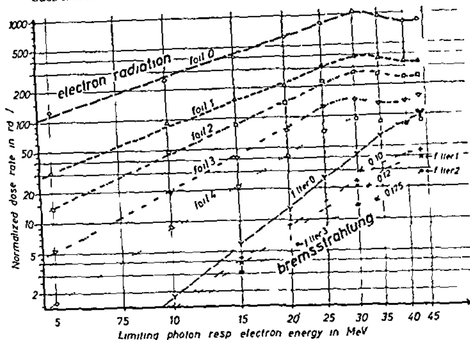


Fig 1 Normalized dose rate in the beam axis as a function of energy for electron radiation and bremsstrahlung

mum energy without homogenizing filter (the so called reference dose rate) both measured at the same FSD with the field confined to the maximum useful field angle $\alpha = 0.167$. Owing to the normalization it was possible to reproduce the dose rates of the curves within surprisingly narrow limits of tolerance these were mostly considerably lower than 10 % an accuracy not only maintained on subsequent days but even at intervals of one year and despite the use of different cathodes. The absolute dose rate values are arrived at by multiplying the normalized values with the reference dose rate measured only once.

2 *Dose rate as a function of energy* The dose rate as a function of energy for electron radiation and bremsstrahlung in normalized units is shown in Fig 1. According to definition the value of the bremsstrahlung without filter (filter 0) for 43 MeV and maximum field has been taken as 100 %.

The dose rate D of the electron radiation in the beam axis strictly follows an exponential law in the form $D \sim E$ for all scattering foils up to energies of $E = 30$ MeV because with double logarithmic representation rectilinear lines

Table 2

Exponents n of the exponential dependence $D \sim E^n$ of dose rate D and energy E for various foil thicknesses (electron radiation) or homogenized field sizes (bremsstrahlung). n absolutely valid up to 30 MeV

Type of radiation	Electron radiation					Bremsstrahlung			
Foil/filter	0	1	2	3	4	0	Energy depending		
Foil thickness (mm)	0.0	0.10	0.25	0.60	1.20				
Useful field angle α (radians) for circular fields						0.0	0.10	0.12	0.175
Exponent n	2.37	1.98	1.66	1.40	1.24	2.87	2.43	2.40	2.27

with the gradient n are obtained (n = positive, real number as an exclusive function of the foil).

The bremsstrahlung in the beam axis without filter (filter 0) also obeys the above mentioned exponential law accurately up to 30 MeV and with good approximation up to 13 MeV. The curve, termed "filter 0" in Fig. 1, is the only directly measurable one. It belongs to the primary radiation coming from the small platinum target which acts as anode. The other curves (α = 0.10, 0.12, 0.175) are additionally influenced by the field homogenizing filters and follow the same exponential law, although with another exponent, n. These curves are not directly measurable, because each energy and maximum homogenized field size would be associated with a certain filter shape. The development of the curves plotted from the measured values is dealt with in section 4 "field homogenization". The maximum obtainable dose rate of bremsstrahlung for each energy lower than 13 MeV and, by interpolation for all desired homogenized field sizes, can readily be obtained.

The ascertained exponents n are compiled in Table 2. It may be observed for comparison that SCHITTENHELM (1958) estimated the exponent to amount to 2.8 for the energy dependence of unfiltered bremsstrahlung, based on the efficiency of the generated bremsstrahlung and the angle distribution.

3. *Dose rate as a function of field size.* With electron radiation the dose rate in the beam axis and the depth of the dose maximum are not influenced to any significant extent by the field size, except for minimum useful fields, provided both energy and scattering foil remain unchanged.

Things are different with bremsstrahlung. If the field size is reduced, while

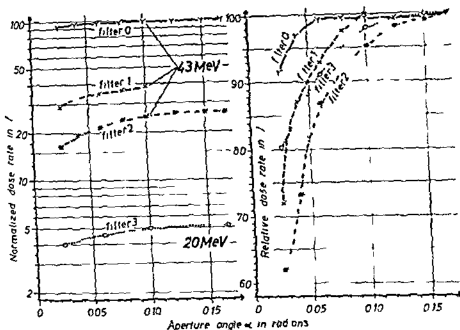


Fig 2 Dose rate in the beam axis as a function of field size (aperture angle α) for bremsstrahlung

all other radiation conditions are kept constant the dose rate in the beam axis drops off systematically

This interrelationship is presented in Fig 2a in normalized units of the dose rate at 43 MeV for non homogenized field (filter 0) and homogenized square fields up to $\alpha = 0.10$ (filter 1) or $\alpha = 0.167$ (filter 2) as well as of the dose rate at 20 MeV up to $\alpha = 0.167$ with filter 3 In contrast to the usual meaning of α as the angle of useful field Fig 2 gives all dose rates as measured in the beam axis with the field sizes reduced to values corresponding to the given aperture angles of α

The results of the same measurements plotted again in relative units, but referred to a maximally homogenized field for each filter (with filter 0 referred to $\alpha = 0.167$) are given in Fig 2b

4 *Field homogenization and dose rate* In electron radiation the relative dose distribution vertical to the beam axis must be investigated to obtain the maximum dose rate for every homogenized field size In contrast to the bremsstrahlung no axially symmetrical dose distribution exists around the beam axis Since the electrons are emitted preferentially in the plane of the accelerati

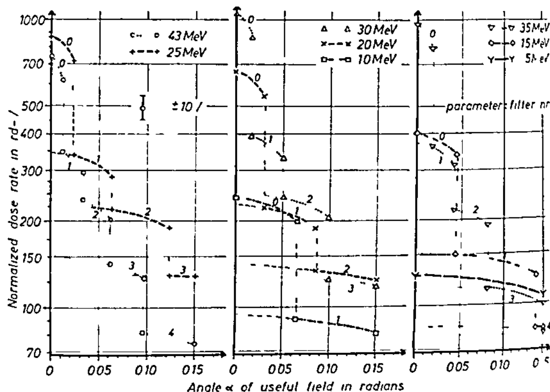


Fig 3 Field homogenization perpendicular to the nominal orbit plane for electron radiation (maximum ± 10 % dose fluctuation within the homogenized field) The maximum dose rate occurs in the application ranges of the scattering foils drawn out in bold dotted lines

path, i e the 'nominal' orbit, it is especially the homogenization of the fields perpendicular to this nominal orbit plane that is critical For this reason, the relative dose distribution was measured only in this direction and always with a maximum field (cone 20 cm × 20 cm at 120 cm FSD, i e $\alpha = 0\ 167$) in the depth of the dose maximum

The dose distribution patterns are plotted in Fig 3, in normalized units of the dose rates for all primary electron energies of practical importance, but for the sake of clarity only the values leading to homogeneous fields were picked out The complete results have been indicated elsewhere (RASSOW 1968) A field in electron radiation is regarded as homogeneous up to the size for which the dose measured in the depth of the dose maximum deviates from the mean value by only ± 10 % or from the maximum value by − 20 %

The thickly outlined curve sections in Fig 3 are those leading to maximum dose rates, while the thinly outlined curve branches correspond to fields that, at the expense of the dose rate, are better homogenized than is possible with weaker scattering

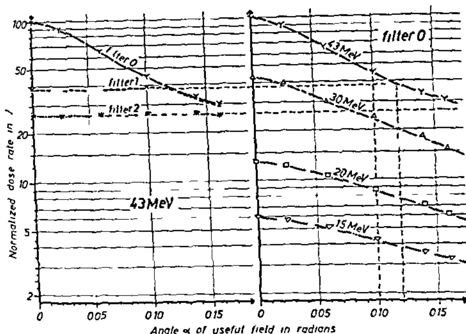


Fig 4 Dose rate profiles for bremsstrahlung filter 0 maximum field sizes and different energies and illustration of the field homogenization by conic absorption filters (Maximum ± 5 % dose fluctuation in the homogenized field)

With bremsstrahlung the problem of field homogenization is different from that existing with electron radiation This can be clearly illustrated by considering Fig 4 Inhomogeneous bremsstrahlung of 43 MeV limiting photon energy is characterized by an almost axially symmetrical dose distribution around the beam axis (filter 0) (Fig 4a) Field homogenization is achieved by attenuating bremsstrahlung by means of a suitable lead homogenizer in the various radiation directions to an extent that would correspond to the dose rate at the periphery of the largest field to be homogenized Filter 1 according to Fig 4 leads to homogenized circular fields up to $\alpha = 0.12$ and filter 2 does so up to $\alpha = 0.175$ With rectangular fields the homogenized linear dimensions of the useful field angle α is supposed to be roughly 20 % below those of circular fields Only in the corners of the rectangular fields dose the homogeneity no longer keep within the tolerance limits of ± 5 %

The corresponding dose distribution curves for inhomogeneous bremsstrahlung are reproduced for four energies in Fig 4b The values of normalized dose rates for differently large homogenized circular fields can be read directly

Table 3

Half value angles $a_{1/2}$ for electron radiation and comparison with calculated values

No of the scatter foil	0		1		2	
Foil thickness d_{1b} (mm)	0		0.1		0.25	
	$a_{1/2}$ in	$a_{1/2} \cdot E$ in	$a_{1/2}$ in	$a_{1/2} \cdot E$ in	$a_{1/2}$ in	$a_{1/2} \cdot E$ in
Energy E in MeV	degrees	degrees ×MeV	degrees	degrees ×MeV	degrees	degrees ×MeV
10	6.4	64				
15	4.1	61				
20	3.05	61				
25	2.48	62	6.8	170		
30	2.0	60	5.6	168		
35	1.68	58	4.4	154	8.9	312
40	1.53	61	4.2	168	7.4	296
43	1.43	61	3.7	160	7.0	301
Calculated as $K_{1b}(d_{1b}+d^{\circ}_{1b})$		(61)		161		311

Table 4

Half value angles $a_{1/2}$ for bremsstrahlung and theoretical values $Oa_{1/2}$ calculated by KULENKAMPFF *(1944)*

	Measurement		Anode thickness 0		Anode thickness $R_{1/2}$		
E in MeV	$a_{1/2}$ in degrees	$a_{1/2} \cdot E$ in degrees ×MeV	$Oa_{1/2}$ in degrees	$Oa_{1/2} \cdot E$ in degrees ×MeV	$Oa_{1/2}$ in degrees	$Oa_{1/2} \cdot E$ in degrees ×MeV	$\frac{Oa_{1/2}(R_{1/2})}{a_{1/2}}$
15	11.0	165	4.0	60	21.2	317	1.92
20	8.5	170	3.0	60	16.7	334	1.96
30	6.5	195	2.0	60	11.8	353	1.82
43	5.2	223	1.4	60	8.5	362	1.64

Perpendicular lines have been added for the useful field angles $a = 0.10$, 0.12 and 0.175 circular fields. The normalized dose rates thus obtained were plotted versus energy in Fig. 1. This energy dependence has already been discussed. The normalized dose rate measured directly for 20 MeV, with filter 5 fits extremely well into the graphically ascertained curve for $a = 0.175$ in Fig. 1.

5. *Beam divergence and half value angle $a_{1/2}$.* The half value angles $a_{1/2}$ at which the dose rate drops to 50 % of the value in the beam axis may be gathered

Table 5

Reference dose rates for bremsstrahlung without filter at maximum field and 100 cm FSD in the dose maximum

Site of installation	Type	Reference dose rate in rd/min
Gothenburg	BBC	98
Lund	BBC	130
Helsingfors	BBC	115
Aarhus	BBC	82
Örebro	Siemens	330
Essen (1967)	Siemens	570
(1968)		440

from the complete series of measurements (see RASSOW 1968) that supplement the data furnished in Fig 3 In Table 3 are presented the results with electron radiation for all energies E and the scattering foils with which the half value angle $d_{1/2}$ was measurable within the maximum field size determined by the design of the betatron

The resulting reciprocal proportionality between $a_{1/2}$ and E and a constancy of the product $(a_{1/2} \times E)$ respectively shows a surprising accuracy Values for this product are quoted in the last line of Table 3 which result for the columns of foils No 1 and No 2 from the following empirical formula

$$\frac{a_{1/2} \times E}{(d_{Pb} + d'_{Pb})} = k_{Pb}$$

with $k_{Pb} \approx 1\,000$ degrees $\times$ MeV $\times$ mm^{-1} where d_{Pb} is the thickness of the scattering foil of lead in millimeters d'_{Pb} is a constant that takes care of the natural beam divergence of the deflected electrons and the scattering in the 0 05 mm thick vacuum window of copper through which the electrons issue from the accelerating tube The value of d'_{Pb} is 0 061 mm obtained without scattering foil from the column of foil 0 in Table 3 The agreement between the values computed for foils 1 and 2 and the measurement results is noteworthy

The constancy of the product $(a_{1/2} \times E)$ is only approximate for bremsstrahlung (compare Table 4) This is also to be expected from the theoretical calculations made by KULENKAMPFF (1944) because the process of diffusion and deceleration of the electrons inside the anode material intensifies considerably with increasing thickness of the anode

With reference to the mentioned theoretical considerations the solid angle

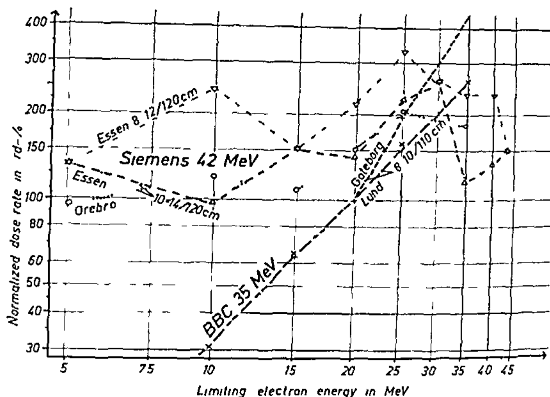


Fig 5 Electron dose rate as a function of energy for various betatrons and homogenized fields

$\Omega_{1/2}$ is introduced, under which half of the entire bremsstrahlung falls, and the resulting plane angle $O_{1/2}$ is defined by the relationship $\Omega_{1/2} = (2O_{1/2})$

Basically, a quantitative comparison of $O_{1/2}$ with the half value angle $\alpha_{1/2}$ measured on the occasion of these tests is not possible because the collimating system of the Siemens 42 MeV betatron allows measurements to be effected only at a useful field angle of maximum $\alpha = 0.167$ However, if by way of approximation, the Gauss distribution is taken as a basis for the directional dependence of the bremsstrahlung it can at least be concluded that a proportionality exists between $O_{1/2}$ and $\alpha_{1/2}$ and hence an identical energy dependence

A rough analysis of the values both measured and computed in Table 4, and the energy dependence of the relationship $O_{1/2}$ $(R_{1/2})/\alpha_{1/2}$ indicates that the platinum pin of the Siemens betatron, which forms the anode averages a slightly larger thickness than $R_{1/2}$, where $R_{1/2}$ is the anode thickness in which half of the electron energy is converted by the ionization and generation of bremsstrahlung

6 *Comparison of the dose rates produced by Siemens 42 MeV betatrons and those yielded by BBC 35 MeV betatrons* VIKTERLÖF (1966) reported on absolute dose

rates of certain Scandinavian 35 MeV betatrons of BBC and his 42 MeV betatron of Siemens at Örebro Since the reference values of the dose rate for bremsstrahlung without filter for maximum energies are unavailable, the present writer decided to estimate these from the dose rates for homogenized fields of various sizes on the basis of plausible suppositions and adjust them mathematically to a FSD of 100 cm These values are presented in Table 5

The dose rates for electron radiation computed from absolute values are shown in Fig 5 A possible minor error in estimating the reference dose rates would reveal itself in the form of a slight vertical shift of the entire curve in the logarithmic representation The typical features determined by different designs of the magnet yokes of the Siemens and BBC betatrons may be recognized at a glance The overall energy dependence of the electron dose rate (with a stationary homogeneous field of 10 cm × 14 cm at 120 cm FSD, or 8 cm × 10 cm at 110 cm FSD) with allowance for the required exchange of the scattering foils amounts to the following values Siemens 42 MeV betatron roughly $D \sim E^{0.3}$ and the BBC 35 MeV betatron roughly $D \sim E^{0.5}$

As normalized dose rates at high electron energies are in the same order of magnitude (the absolute reference dose rates of the Siemens betatrons are roughly three times higher according to Table 3) the steeper drop of the dose rate of the BBC betatrons as the energy decreases is found to be extremely disturbing so the that the BBC betatrons for energies lower than 15 MeV produce highly unsatisfactory intensities

SUMMARY

The maximum dose rates for the 42 MeV betatron in the range of photon and electron energies within 5 and 43 MeV and all field sizes and homogenizing filters have been determined Half value scatter angles and thicknesses of scatter foils are discussed A comparison is made of the energy dependence and absolute values of maximum dose rates of the Siemens 42 MeV betatron and the BBC 35 MeV betatron

ZUSAMMENFASSUNG

Die maximalen Dosisleistungen des Siemens 42 MeV Betatrons werden im Energiebereich von 5 bis 43 MeV fur Brems und Elektronenstrahlung und alle Feldgrossen und Streufolien bzw Ausgleichsfilter bestimmt Die Halbwertstreuwinkel sowie die optimalen Streufolendicken werden diskutiert und fur das Siemens 42 MeV und das BBC 35 MeV Betatron Energieabhangigkeit und absolute Werte der maximalen Dosisleistungen verglichen

RÉSUMÉ

L'auteur a calculé les débits de dose du bétatron de 42 MeV dans le domaine des énergies photoniques et électroniques entre 5 et 43 MeV, pour toutes les dimensions de champ et avec des filtres homogénéisants. Il examine les angles de diffusion de demi absorption et de l'épaisseur des filtres. Il donne une comparaison de la dépendance vis-à-vis de l'énergie et des valeurs absolues des débits de dose pour le bétatron de Siemens de 42 MeV et le bétatron BBC de 35 MeV.

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DOSE RATE MEASUREMENTS IN BLADDER AND RECTUM

Intracavitary radiation of carcinoma of the uterine cervix

by

INGEMAR JOELSSON and ANDERS BACKSTROM

Attempts were made as early as the beginning of this century to obtain information on the amount of radiation absorbed in the tissues as a result of radiation therapy A colorimetric method was introduced by HOLZKNECHT in 1910 while others employed iontoquantimeters (SEITZ & WINTZ 1920) SIEVERT was among the first to use ionization chambers and in 1932 he established this technique by *performing* rectal measurements in patients with carcinoma of the uterine cervix treated at Radiumhemmet A number of methods for the registration of dose rates have since been developed (FARMER 1945 BOMBKE & EBERLE 1949 RIES 1949 TURNER & NEWBERRY 1950, and FLETCHER 1953) The first dosage ratemeter used clinically at Radiumhemmet (WALSTAM 1954) was similar to the one described by TURNER & NEWBERRY

According to the current Stockholm technique dose rate measurements in the bladder and rectum are an everyday practice The values obtained are used as a basis for the determination of treatment time Unexpectedly high dose

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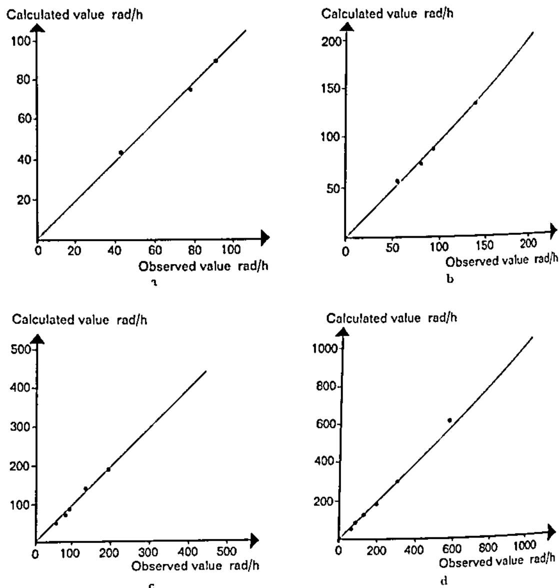


Fig 1 Calculated dose rates compared with the values observed within the sensitivity ranges of 0—100 rad/h (a) 0—200 rad/h (b) 0—500 rad/h (c) and 0—1 000 rad/h (d) Each symbol indicates the mean of three observations

rates or the observation of a maximal dose rate at a distance from the orifice of the urethra or the sphincter of the anus, improbable from an anatomical viewpoint will indicate that the irradiators are incorrectly placed and that re insertion is necessary

The development in recent years of solid state dosemeters has made feasible a

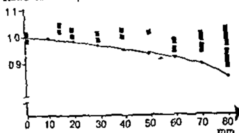


Fig 2 The ratios of readings in water/in air of the Siemens Gammameter at distances between 15 and 80 mm from the center of the measuring probe to the radium source Vertical bars indicate the variation at each point the dotted arrow points to the result of BATHO & YOUNG

implified design in which small detectors of cadmium sulphide are utilized These instruments yield satisfactory recordings of exposure rates even in the presence of steep dose rate gradients The Siemens Gammameter is a commercially available cadmium sulphide dosemeter fitted with a direct reading moving coil ammeter The scale is calibrated in rad/h and five dose ranges are available by series-parallel switching of resistors The sensitive volume consists of two parallel discs of cadmium sulphide centered in a gold housing the thickness of each disc being 0 05 to 0 3 mm and the area 4 to 6 mm $\times$ 3 mm The dimension of the entire detector is 4 5 mm $\times$ 20 mm To facilitate measurements in the center of the true pelvis the detector of the instrument used at Radiumhemmet is placed at the end of a slightly curved sound of stainless steel 20 *cm in length* with a wall thickness of 0 5 mm

As has been emphasized by FOWLER (1963) radiation falling on a cadmium sulphide detector leads to an increase in the number of free electrons in the conduction band of the atoms whereby the electric conductivity is enhanced In comparison with a strictly behaving solid state ionization chamber the induced current is 3 to 4 orders of magnitude higher The linearity of the induced current with respect to the exposure rate is good The relationship follows a 0 95 $\pm$ 0 05 power law up to exposure rates of at least 2 000 R/h The response time of the cadmium sulphide crystal decreases with increasing exposure rate but this relationship is not strictly proportional At low exposure rates the rise and decay times are not necessarily equal and depend on the previous exposure rates and the storage temperature The decay time after 1 R/h gamma irradiation is 30 to 100 seconds for 9/10 of total reading A corresponding decay time at 10 R/h exposure rate is 10 seconds and at 100 R/h exposure rate it is only about one second

The rise time of the instrument can be very long at low exposure rates after long periods without irradiation This may be overcome by maintaining a con

tinuous low exposure rate for the cadmium sulphide crystal during storage This treatment is known as 'priming' (TURNER, MASH & FOWLER 1963)

For a rate meter to have wide application its response must be only slightly dependent on the incident radiation energy Cadmium sulphide crystals are energy dependent, the response is greater to photon radiation of low energy Single crystals can be 50 times more sensitive to roentgen rays at 50 keV than at 1 MeV (FOWLER 1963) It is possible greatly to reduce this energy dependence by using shields of high density metals around the crystal (HOLLANDER 1957, JONES 1960)

The performance characteristics of the Siemens Gammameter at Radiumhemmet has been studied with special reference to linearity, quality and dose rate gradient dependence, temperature dependence and the effect upon rise time of a change in temperature and break in priming The radial and longitudinal directional sensitivity have also been investigated In all these tests, the sensitive volume was enclosed in the stainless steel sound The orientation of the discs of cadmium sulphide relative to the curvature of the sound was not determined

Linearity The reading of the instrument was observed for different dose rates within each of four sensitivity ranges of the instrument by using a cobalt 60 radiation source The exposure rate at a distance of one meter had been determined by employing a substandard calibrated Baldwin Farmer dosemeter, and the dose rates at a number of specified points along the central axis were computed to an accuracy of ±0 5 % by the inverse square law and the conversion factor (FALMER 1942, 1945, NUTTAL & SPIERS 1946, SIEVERT 1947) The gammameter probe was positioned at each of the points to an accuracy of ±1 cm The deficiency in precision in the placement of the probe caused an error of less than 1 % in the exposure rate values Four to eight dose rates within each sensitivity range of the instrument were studied In no instance did the difference between the observed and calculated values expressed as percentages of the calculated values exceed −8 % or +7 % (Fig 1)

Quality and dose rate gradient dependence The energy dependence of the cadmium sulphide crystal of the Siemens Gammameter is reduced by a gold filter The inhomogeneity introduced in a radiation field by a measuring probe induces displacement of the isodose curves, especially when the dose rate gradient is steep Even if the radiation from a radium source is the same, irrespective of whether it is located in water or in air, the change in the spectral distribution of the radiation in water will be markedly different from that in air, due to absorbtion and scattering Both the quality and the dose rate gradient dependence have to be studied together by observing the response of the cadmium sulphide crystal in water and in air for various distances between the center of the measuring

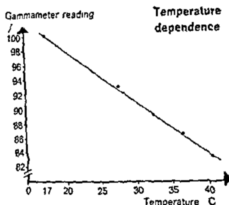


Fig 3 Change n readings (as percentage of base level alue) of the S emens Gammameter mmersed in a water bath with the probe r ng n temperature from 17 0 to 40 3 C at constant exposure

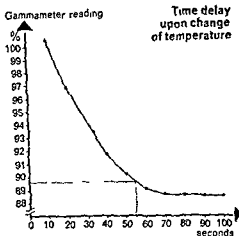


Fig 4 Change in readings of the Gamma meter with time after immersing probe in water bath of about 37 C temperature Ex posure of CdS crystal was kept constant The reading at room temperat ire (?1 3 C) which represents the base value is standardized to 100 The 90 total change (8.7 change in read ng) was reached after 55 seconds

probe and the radium source In this case readings were made at distances from 15 to 80 mm and the results were expressed as the ratio of the readings in water in air The same ratio has been investigated by others using a quality independent ionization chamber (BATHO & YOUNG 1964) The values obtained in the present study are given in Fig 2 together with other published data It may be seen that while within 40 mm distance the values are close to 1 0 correc tions of up to 5 % are needed for a distance of 80 mm

The response of the cadmium sulphide crystal of the Siemens Gammameter to radium and cesium irradiators in polymethyl metacrylate at distances of 30 and 40 mm was also studied The figures representing the ratio Ra reading/Cs reading were compared with the calculated ratios using the figure of specific gamma ray emission from Ra, $\Gamma = 0\ 83$ R m g^{1} h^{1} at 1 m and that of the emission from ^{137}Cs $\Gamma = 0\ 33$ R m Ci^{1} h^{1} at 1 m (ICRU 1963) The ob served ratios mean of five observations were $2\ 65 \pm 0\ 16$ and $2\ 73 \pm 0\ 16$ at 30 and 40 mm distances and the resulting differences between calculated and observed values were +6 % and +9 % These figures suggest that the cadmium sulphide crystal is more sensitive to the energies of the gamma rays from radium than the energy from cesium

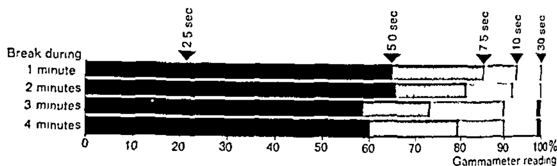


Fig 5 Differences in rise time of the gammameter after a time interval between priming (at 22 C) and dose rate measurement (at 37 C) of 1 to 4 minutes Readings are listed as percentage time in seconds Nine tenths of full deflection was reached in about 10 seconds

Temperature dependence The change in sensitivity of the instrument was studied with the gammameter probe immersed in a water bath and subjected to a change in temperature from 17 0 to 40 3 °C at a constant exposure rate in the range of 200 R/h The dose rate reading was lowered by 0 7 % per degree centigrade (Fig 3) This implies that if the gammameter is calibrated at a temperature of the probe of about 22° C the reading with the probe at 37° C will be only 90 % of the correct value

Another facet of the temperature dependence of the crystal is represented by the time delay until stability in reading is reached, i e when the temperature of the gammameter probe is being changed The following study was therefore made The probe was immersed in a 37° C water bath, keeping the exposure rate constant at about 50 R/h, and the readings at every 10th second were noted It was found that 9 10th of the total change in deflection was reached after about 55 seconds (Fig 4)

The gammameter probe, when in daily use, is stored at room temperature and exposed to radiation at a low exposure rate The priming will necessarily have to be discontinued for a few minutes during preparation of the probe for insertion into body cavities The effect of this upon the delay in response of the instrument was studied When the break in priming lasted up to 4 minutes, 9/10th of the full deflection was reached in about 10 seconds After 30 seconds the remaining error was only 1 % (Fig 5)

Radial and longitudinal directional sensitivity The radial directional sensitivity of the probe with its cadmium sulphide crystal was studied in water, using a polymethyl metacrylate fixture, thereby securing a reproducible interrelationship between the irradiator and the probe The readings of the instrument were observed for 45° stepwise rotations of the probe around its central axis Three

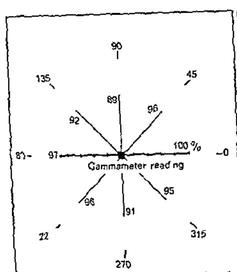


Fig 6 The reading of the Siemens Gammameter as percentage (mean of three observations within different dose rate ranges) relative to the radial rotational departure of the probe from the position with the irradiator in the plane perpendicular to its concavity

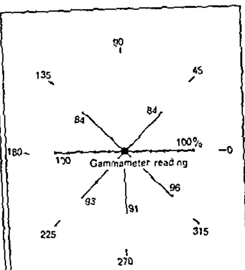


Fig 7 The reading of the gammameter as percentage (mean of three observations within different dose rate ranges) relative to the longitudinal rotational departure of the probe from a position with the irradiator in the plane perpendicular to its concavity

different dose rates were used The reading obtained when the irradiator was located in a plane perpendicular to the concavity of the probe was standardized to 100 % The angular relationship between the discs of the sensitive volume and this plane was not determined The readings were found to be asymmetrically distributed which is probably a reflection of the eccentric position of the discs in the crystal The variation in reading for a change in orientation of 360° was ±6 % (Fig 6)

The longitudinal directional sensitivity of the gammameter probe was studied in a similar fashion The reading of the gammameter was recorded for every 45° rotation of the probe about the transverse axis through the center of the sensitive volume Standardization to 100 % was made for the same condition as above Increased absorbtion in the stainless steel sound and in the gold housing for orientations away from this position is responsible for the variation in reading of ±8 % (Fig 7) The sensitivity was not investigated within the sector between 45 and 135 including the so called solid angle

Performance characteristics of the Siemens Gammameter In routine use the error due to insufficient linearity of the gammameter is about ±2 % The error

amounts to as much as ±7 % only in the neighbourhood of 1 000 rad h The dependence of the crystal on the quality of the radiation, and the inhomogeneity of the radiation field induced by the measuring probe, can be neglected within the distances from the radioactive sources encountered in the clinic The sensitivity of the cadmium sulphide crystal was found to be higher to radiation from radium than from cesium, which necessitates the use of correction factors when the radiation from cesium is measured If the instrument is calibrated with the crystal at room temperature, the readings at body temperature will need to be corrected Thus, at least one minute should be allowed for temperature stabilization If this principle is adhered to, the effect of a break in priming will be of no consequence The radial orientation of the probe in the radiation beam can induce an error of up to ±5 % The error is probably less since the concavity plane of the curved probe should always be kept as close to the sagittal plane of the patient as possible The longitudinal orientation of the probe relative to the irradiators inserted in the body, on the other hand, depends on the anatomy The error induced by variation in longitudinal orientation can amount to ±8 % The errors in basic calibration, including the possible misreading of the instrument, amount to ±3 % The conclusion is that the resulting probable error amounts to about ±10 %

Clinical application The pertinent question was whether dose rates measured in a subject in the lithotomy position truly represent the radiation dose absorbed during treatment of the patient when lying supine in bed

Twenty six patients with carcinoma of the uterine cervix in stages I b to III, from a consecutive series, were studied in conjunction with the first or second radium applications

With the patient in lithotomy position following the insertion of the radium the centimeter graduated probe of the Siemens Gammameter was introduced in the urinary bladder through the urethra Starting 12 to 13 cm cranial to the orifice of the urethra the dose rates were determined for every centimeter along the base of the bladder and the urethra during withdrawal of the probe The long axis of the probe was carefully maintained parallel with the sagittal plane of the patient and the tip of the probe kept in close proximity to the uterine body and cervix The mean value of the three highest consecutive figures obtained was used as a measure of the maximum dose rate at the base of the bladder The distance from the orifice of the urethra to the middle of these positions of the probe was used to define the location of the area of highest dose rate of clinical significance Similar measurements and analogous computations were carried out with respect to the rectum and the sphincter of the anus The measurements were in all instances carried out by one of the authors (I J)

Table

Individual differences in dose rates between measurements in lithotomy and supine positions as percentages of values obtained with the patient in lithotomy position. P was determined according to the student's t test. Degrees of freedom = 25

	Difference in dose rate as percentage of lithotomy position value	
	Urinary bladder	Rectum
	+13	+34
	+19	+ 1
	+ 3	— 2
	+24	— 2
	+27	+14
	— 3	+16
	+23	+ 5
	+21	—14
	—14	— 4
	+37	— 3
	+ 4	— 8
	—12	— 4
	— 2	—13
	+13	— 2
	+ 6	—47
	+65	— 4
	— 2	—19
	+36	+22
	+ 5	+ 5
	+ 8	— 3
	+12	0
	+ 1	—18
	+ 7	—29
	+26	—14
	— 7	— 4
	— 3	— 2
Limits	—14 and +65	—47 and +34
Mean	+12	— 3
S E	3 4	3 1
P	0 001 < p < 0 01	0 2 < p < 0 3

Routinely performed dose rate measurements in lithotomy position were followed by measurements after the patient had been placed in the supine position, anesthesia being maintained The differences between the mean values of the three highest dose rates in the bladder and rectum, in lithotomy and supine positions, were calculated for each patient as percentages of the lithotomy position values (see Table)

The mean difference in dose rates at the posterior wall of the urinary bladder between the measurements in lithotomy and supine positions amounted to +12 % (S E = 3 4) The range of differences was large and the limits registered were — 14 % and +65 % In about a third of the patients the difference amounted to more than +20 % and a tenth of the patients exhibited differences above +30 %

The mean difference in dose rates at the anterior wall of the rectum, between measurements in lithotomy and supine positions, was — 3 % (S E = 3 1) The range of differences was about the same as in the bladder measurements with a lowest value of —47 % and a highest value of +34 % For four of the patients the difference was above +20 % and in only two patients out of twenty six did the difference exceed +30 % This means that the dose rate at the base of the urinary bladder was on an average higher in the supine than in the lithotomy position A corresponding difference between the mean values of the dose rates at the anterior wall of the rectum in supine and lithotomy positions was no observed

The individual differences in distance from the orifice of the urethra and from the sphincter of the anus to the areas of dose rates of clinical significance between lithotomy and supine positions were calculated The displacement of the area of highest dose rate from its lithotomy position value was insignificant although in individual cases the range of values along the posterior wall of the urinary bladder was — 20 to +30 mm and along the anterior wall of the rectum — 20 to +20 mm The following two case reports serve to illustrate the findings

Case I A 40 year old gravida IX with stage II b carcinoma of the cervix The difference in highest dose rates between measurements in the bladder in lithotomy and supine positions was + 65 % The tumor was of cauliflower type and involved the anterior and left lateral fornices the left paracervical tissue was also involved

Two irradiators in tandem each containing 43 mg of radium were chosen for the uterine cavity A flat box containing 72 mg of radium was placed in the vagina and kept against the tumor by means of a gauze pack According to measurements performed in lithotomy position the treatment time was determined at 27 hours with a maximal dose of 2 000 rad to the bladder and 2 050 rad to the rectum during the first course of treatment After the patient had been placed in supine position the mean dose rate in the bladder was found to be 65 % higher and the one in the rectum 4 % higher than in the former measurements The measurements in treatment position thus indicated that during the



Fig 8 Lateral roentgen films in lithotomy position (a) and supine position (b) during dose rate measurements in the bladder The probe is in the position that gave the highest reading

first course the dose at the bladder base amounted to 3 300 rad and the dose at the anterior wall of the rectum to 2 100 rad

After a second course of intracavitary radiation (1 200 rad to the bladder and 1 700 rad to the rectum) and external ^{60}Co therapy (dose to the parametrium 4 500 rad) the condition of the patient was satisfactory She never complained of urinary disturbances At an examination 3 months after the first course of treatment complete regression of the tumor was recorded

Case 2 A 44 year-old gravida III with carcinoma of the cervix stage II b The difference in dose rates in the bladder between measurements in lithotomy and supine positions was +24 % The growth was of an excavating ulcerating type

The patient was treated with 86 mg radium in the uterine cavity and 72 mg radium in a curved box in the vagina for 22 hours in the first course of treatment with 1 850 rad to the bladder and 1 950 rad to the rectum After three weeks the patient had for 15 hours an intra uterine irradiator containing 70 mg radium and a flat box with 71 mg radium in the vagina firmly positioned against the edges of the ulcer by means of gauze packing According to dose rate measurements in lithotomy position the dose in the bladder amounted to 1 400 rad while measurements in supine position indicated 1 750 rad Corresponding doses in the rectum were 2 250 rad and 2 700 rad One month later external ^{60}Co therapy was begun and 5 000 rad was given to the parametrium over six weeks

Ten months after commencement of therapy the patient was without symptoms and examination failed to reveal any signs of tumor

Roentgen films in lithotomy and supine positions were obtained for Case 2 during dose rate measurements in the bladder and rectum (Figs 8 and 9) The probe of the gammameter was kept in place during the exposures for registering the maximal dose rate In lithotomy position despite the use of a curved steel



Fig 9 Lateral roentgen films in lithotomy position (a) and supine position (b) during dose rate measurements in the rectum The probe is maintained in the position that gave the highest gammameter reading

ound, the sensitive volume of the probe did not reach down to the center of the space between the vaginal and intra uterine irradiators, where the isodoses intersect to form the hot point In contrast to this it was noted that during the dose rate measurements in the rectum the sensitive volume of the gammameter probe easily passed as close to the V shaped proximity of box and cylinder as the thickness of the intervenient tissues allowed Unfortunately, the exposure of the personnel made it impracticable to perform radiography routinely during the dose rate measurements

One of the means to avoid untoward reactions in the mucosa of the bladder and rectum is to introduce distance increasing materials around the irradiators The vaginal box is generally kept at a distance from the anterior wall of the rectum by gauze packing This should ideally produce an even dose distribution at the base of the bladder and the anterior wall of the rectum Discharge and secretions from the uterus during the treatment can be expected to macerate the gauze material thereby reducing its volume, with a consequent increase in dose rate at the anterior wall of the rectum

The dose rates at the base of the bladder and at the anterior wall of the rectum, in the supine position, obtained immediately after radium application were compared with the similarly obtained values just before withdrawal of the irradiators in a consecutive series of ten patients It was found that the dose rate in the urinary bladder at the end of treatment computed from the individual mean values and expressed as a percentage of the application values, had decreased by 9 % (S E = 7 0) The range was from — 52 % to + 30 % Only

two of the patients exhibited differences in positive direction The dose rate increment in the rectum at withdrawal of the irradiators was 26 % (S E = 8 6) The lowest value of difference was — 8 % and the highest +55 % In six of the ten patients the increase was more than 30 % while in two of them it exceeded 50 % On an average the higher dose rate was registered over an area s ill located at the same distance from the sphincter of the anus Furthermore the area of highest dose rate in the urinary bladder was not displaced in the course of treatment The individual limits were however, — 10 mm to +20 mm

Discussion

The original Stockholm technique of radium therapy in carcinoma of the uterine cervix was founded on experience (HEYMAN 1918 1925 KOTTMEIER 1958) The intracavitary radium treatment was defined in terms of milligram element hours which is a product of the amount of radium administered and the duration of treatment for the uterine and vaginal implants Despite the fact that no information was given regarding the dose absorbed in the tissues the data which were available on the intensity of radioactive sources time factor filtration of radium and active length of irradiators enabled an estimation of the dose distribution in the pelvis provided anatomical differences were not too marked

The current Stockholm technique is characterized by application of radioactive sources to the uterus and the vagina in combination with external radiation to the parametrium and the pelvic wall Two courses of endotherapy are administered with comparatively high activity of the irradiators Dose rates are measured in the bladder and the rectum for adjustment of the treatment times The external radiation was earlier given with conventional roentgen rays (200 kV) In re ent years high energy therapy has been applied routinely in cases of more extensive carcinomas Since 1947 there has been a tendency to individualize the therapy paying regard to several factors such as the type and spread of the tumor width and elasticity of the vagina, and the general condition of the patient GRAY & KOTTMEIER 1957 KOTTMEIER 1964)

At a time when dose rate measurements were not achievable in clinical practice the need to determine the dose of radiation absorbed in the pelvic tissue led to the designation of specific areas paracervically in which the doses were to be specified TOD & MEREDITH 1938) The selection was influenced by the contention that the tolerance to radiation in the paracervical triangle reflects the limiting factor of normal tissue tolerance in the irradiation of the uterine cervix (TODD 1938) Irradiators were constructed in such a way that the isodose curves around them were uniform (TOD & MEREDITH 1953) The use of these irra

diators simplified the practice to deliver a precalculated dose to the paracervical triangle, the center of which was named point A. By definition, point A is located 2 cm cranial to the fornix of the vagina and 2 cm lateral to the center of the cervical canal. The intracavitary radium treatment was signified by the dose at this point. Point A was anatomically considered to be close to the intersection of the ureter and the uterine artery. The center of an area 3 cm lateral to this point representing the interiliac lymph nodes of Leveuf (often called the obturator lymph nodes), was called point B.

It has been shown by INGELMAN SUNDBERG (1947) that the main cause of the rectal injury most likely is a too intense irradiation of the rectum. Appreciating the basic significance of the observations made by the Manchester School (PATERSON 1948) KOTTMEIER does not support the importance to limit the evaluation of the dose to the paracervical triangle. By observing the dose rates and calculating the absorbed doses in the posterior wall of the bladder and the anterior wall of the rectum and correlating the findings with clinical signs of tumor and tissue reaction the possibilities should be enhanced to design an individual treatment. This is particularly true with regard to the fact that the principle of the treatment is to deliver the largest possible dose of radiation to the tumor without causing irreparable damage to the urinary bladder and the rectum.

The clinical importance of dose rate measurements along the posterior wall of the urinary bladder and the anterior wall of the rectum has been established after evaluating the correlation between the dose in the organs (measured as described above) and the complications following radiation (GRAY & KOTTMEIER 1957, KOTTMEIER & GRAY 1961, and KOTTMEIER 1964). In a consecutive series of 500 patients treated according to the Stockholm technique, including the individual variations, these authors measured dose rates in a more careful fashion than is possible routinely, and this with the aim of determining the maximum dose that can be tolerated in the rectum. The correctness of the values obtained was sometimes verified by measurements performed by different observers. In the treatment of patients with advanced tumor the dose was intentionally increased in order to enhance the chances of cure, despite the awareness of the augmented risk of radiation damage. This program also provided the opportunity to analyze the possibility of employing measurements of dose rates in the rectum and in the bladder as guidelines for the clinical management in each individual case. It was found that the safe figures from intracavitary radium amounted to between 4 000 and 4 200 rad in the rectum and to a slightly higher figure in the bladder. It was concluded that the figures do not apply to any other radiation techniques or different measurements of doses.

The findings in this study indicate that dose rate measurements in the bladder, performed in the supine rather than the lithotomy position, would more closely

reflect the highest dose that during treatment could possibly reach the base of the bladder The observed occurrence of higher dose rates in the rectum at the withdrawal of the irradiators than at the insertion leads to the proposal of substituting the gauze material by a more unalterable distance increasing spacer

Conclusion

The instrument has been applied in a clinical study of the differences in dose rates in the urinary bladder and the rectum between measurements performed in the lithotomy and supine positions A mean difference of +12 % in the latter position was observed in the bladder This might be explained by the difference in position of the probe and the bladder wall in relation to the irradiators in the supine position compared with the lithotomy position The dose rate measured at the anterior rectal wall was observed to increase during treatment time by an average of 26 % This difference is ascribed to maceration of the gauze material used for distance increasing purpose

SUMMARY

The performance characteristics of the Siemens Gammameter have been defined through separate testing of linearity quality and dose rate gradient dependence temperature dependence effect of change in temperature and break in priming as well as of the influence of radial and longitudinal orientations of the probe The dose rates in the bladder were observed in a clinical study to be higher in the supine than in the lithotomy position and the dose rates at the anterior wall of the rectum increased with the treatment time

ZUSAMMENFASSUNG

Die charakteristischen Eigenschaften des Siemens Gammameters wurden experimentell durch einzelne Bestimmungen von Linearitat Qualitat Dosisratenabhangigkeit, Temperaturabhangigkeit Effekt einer Temperaturveranderung und break in priming sowie vom Einfluss der radialen und longitudinalen Orientierung der Sonde studiert Beim klinischen Gebrauch zeigte es sich dass die Strahlenintensitat in der Harnblase gemessen hoher in der Ruckenlage als in der Steinschnittlage ist Es zeigte sich ebenfalls dass die gemessene Intensitat an der Vorderwand des Rektums der Behandlungszeit entsprechend ansteigt

RÉSUMÉ

Les caracteristiques de fonctionnement du Gammametre Siemens ont ete definies par des épreuves separees de linearité de dépendance a l'égard de la qualité et du gradient du taux de dose de dépendance a l'égard de la temperature d'influence de changement de la temperature et break in priming et d'influence de l'orientation radiale et longitudinale de la sonde Dans une etude clinique les taux de dose dans la vessie ont ete trouves plus elevés en decubitus qu'en position gynecologique Les taux de dose dans la paroi anterieure du rectum augmentent avec la duree du traitement

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PELVIC DOSIMETRY DURING RADIOTHERAPY OF CARCINOMA OF THE CERVIX UTERI

by

J. M. JOHANSSON, B. Å. A. LINDSKOUG and C. E. NYSTROM

The problem of recording the radiation dose absorbed during radium therapy of carcinoma of the cervix uteri is as old as the treatment itself. Initially attention was focussed on the administration of adequate doses to the primary tumour from radium sources while avoiding excessive doses to surrounding healthy tissue. The present problem is to achieve an optimal distribution of the radiation dose in the pelvis by a combination of intracavitary radium and external megavoltage therapy; this is now the usual treatment in carcinoma of the cervix uteri at the Gothenburg Radiotherapy Centre. The method may be modified by accentuation of the radium treatment in cases of predominating vaginal spread and the external radiotherapy in midpelvic and parametrial involvement.

The basic principles of the method have been described by LEISSNER & NYSTROM (1967). Two or three intracavitary radium applications at 2 week intervals are immediately followed by external treatment with 5 MV roentgen radiation from a linear accelerator. Two opposing double wedge fields, each about 19 cm × 19 cm, are used. The main purpose of this technique is to produce a

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Table 1

Amounts of radium used, number of measurements and measuring times

Case	Intrauterine mg Ra	Vaginal mg Ra	Number of measurements	Measuring time hours
1	80	100	2	4.5 twice
2	30	40	1	17.4
3	80	100	2	5.6 twice
4	60	80	2	4.6 twice
5	60	100	2	5.0 and 6.0
6	60	80	2	6.0 twice

sufficient and homogeneous dose to the regional lymph nodes along the lateral pelvic walls, taking into consideration the additional effect of the intracavitary radium, the dose rate contributed by the radium in this region has been estimated in earlier studies.

LEDERMAN (1950) measured this dose rate by introducing a direct recording instrument against the lateral pelvic wall through the vagina. KOTTMEIER (1951) measured the dose distribution in the pelvis in 20 cases during bilateral lymphadenectomy with the radium still in situ. The measurements were made during combined applications to the uterus and the vagina as well as during treatment of only one of these sites. The measurements were performed at several points in the lateral part of the parametrium and at the lateral pelvic wall on both sides.

GORTON (1953) published measurements (performed in collaboration with SKOLDBORN) in 11 cases of lymphadenectomy during radium treatment. These were made at three points on either side: at the bifurcation of the iliac vessels, the pelvic wall, and the crossing of the iliac artery and inguinal ligament.

WALSTAM (1954) performed isodose measurements of intrauterine and vaginal applicators with a water phantom technique. A similar method was used by KJELLGREN & RAGNHULT (1963) who measured the isodose curves for the permanently loaded applicators developed in Gothenburg.

FABIAN & BENNINGHOF (1966) calculated the dose along the external and common iliac veins with the aid of lymphography. Ten years ago BENNER, KJELLGREN & LEISSNER (private communication) investigated in cadavers the possibility of applying miniature ionization chambers in the large veins of the pelvis for intravasal dosimetry in patients undergoing radium treatment. It was not possible at that time to construct dosimeters of such small size that they could be percutaneously inserted into appropriate veins. It is only recently that thermolumi-

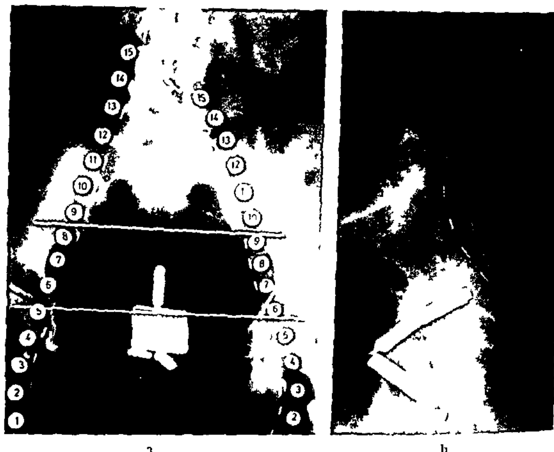
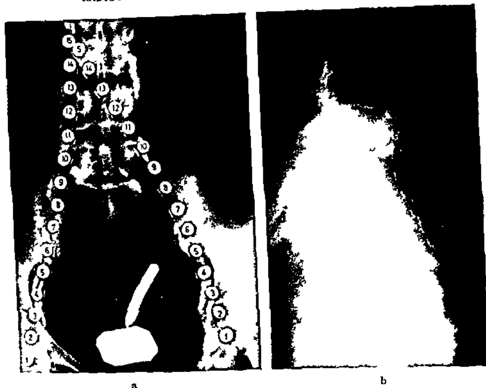


Fig. 1. Case 4. Frontal (a) and lateral (b) projections. Good symmetry of sources and catheters; the straight lines are drawn in the obturator node plane (lower line, plane 1) and the hypogastric node plane (upper line, plane 2).

nescence dosimeters consisting of very small teflon rods as a matrix for lithium fluoride (LiF), made this technique feasible. The technical problems have thus been overcome, making it possible to perform dose measurements in the pelvic veins at several points simultaneously.

Material and Methods. Dose measurements were performed in eight cases of carcinoma of the cervix uteri but two cases were for technical reasons excluded from this report: in one case only one probe could be introduced and in the other the probe had been displaced from its correct position. Two measurements were made in five cases, and complete measurements are therefore reported for 11 instances in all.

The amount of radium, number of measurements and the measuring time are given in *Table 1*.



a b

Fig 2 Case 6 Frontal (a) and lateral (b) projections Marked asymmetry

Immediately before the radium treatment sterile teflon catheters were inserted in both external femoral veins in a cranial direction as far as to the origin of the inferior vena cava These catheters were closed proximally with gold cuplets and served as containers for the indicators and the measuring probes that need not be sterile

In Cases 4 and 6 the catheters were kept in position until the first external radiation treatment had been given

The insertion of the outer catheters into the veins was controlled by a roentgen television monitor probes containing gold indicators in place of dosimeters were inserted to indicate the positions of the dosimeters The sites of the indicators were confirmed by orthogonal roentgenograms before the radium application After the radium had been applied further roentgenograms were taken with the indicators still in place (Figs 1 and 2) The dose measuring probes were then introduced The patient lay on an ordinary bed and was told to remain as still

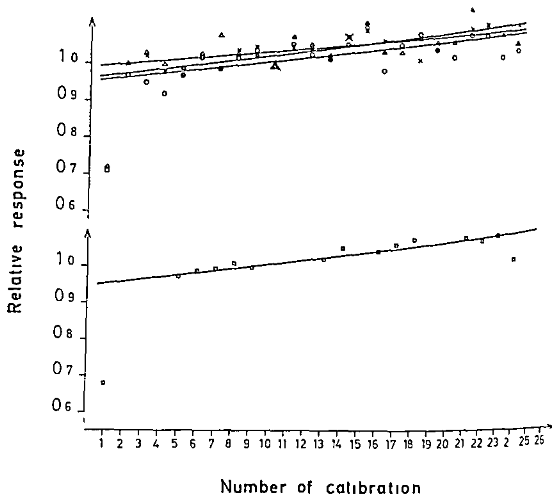
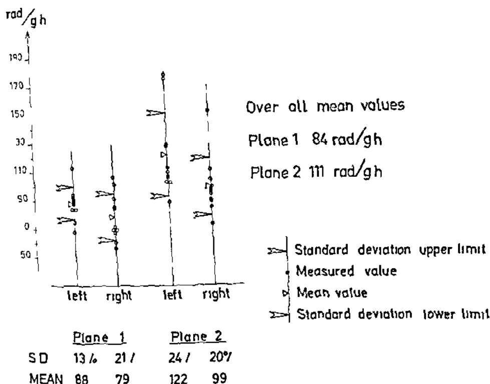


Fig. 3. The upper curves show the relative response of three randomly chosen LiF dosimeters on 24 calibrations to 100 rad ^{60}Co. The values are normalized to the 10th calibration. The lower curve shows the cumulated response of 15 LiF teflon dosimeters on 25 calibration irradiations to 100 rad ^{60}Co normalized to the 9th calibration. The straight lines were calculated by the method of least squares.

as possible. The insertion of the catheters and the probes did not disturb the field distribution of the radiation.

Dosimetry. An introduction to the subject of thermoluminescent dosimetry (TLD) has been given by CAMERON, SUNTHARALINGAM & KENNEY (TLD 1968) and includes a bibliography of about 500 papers. A bibliography has also been presented by LIN & CAMERON (1968).

The first model of the reading device used was described by BENNER, JOHANSSON, LINDSKOUG & NYMAN (1967); a few early measurements were also reported. An improved device, which is now in use, was described by LINDSKOUG, JOHANSSON, KARLSSON & KJELLGREN (1967).



F 4 Dose rates pe gram rad um measured in the external femoral veins The four measur ng points are defined as those where the il ac ve ns cross the transverse planes through the principal ltu ator nodes (plane 1) and the hypogastric nodes (plane 2)

The technique used has made it possible to read off the dosimeters without extracting them from the probes which simplified the individual calibration of each dosimeter The measurements were performed with cylindrical LiF teflon dosimeters 1 mm in diameter and 6 mm in length The dosimeters were inserted into probes of teflon 15 dosimeters in each All the dosimeters were individually calibrated before and after each measurement the calibration being carried out with a dose of 100 rad ^{60}Co gamma rays Each probe was tagged with a colour code The dosimeters were numbered from below and upwards towards the closed end of the probe

The tandard annealing procedure as suggested by CAMERON et coll (1964) cannot be used with this technique as teflon does not resist 400° C To eliminate the rapidly decaying low temperature peaks the dosimeters were heated for

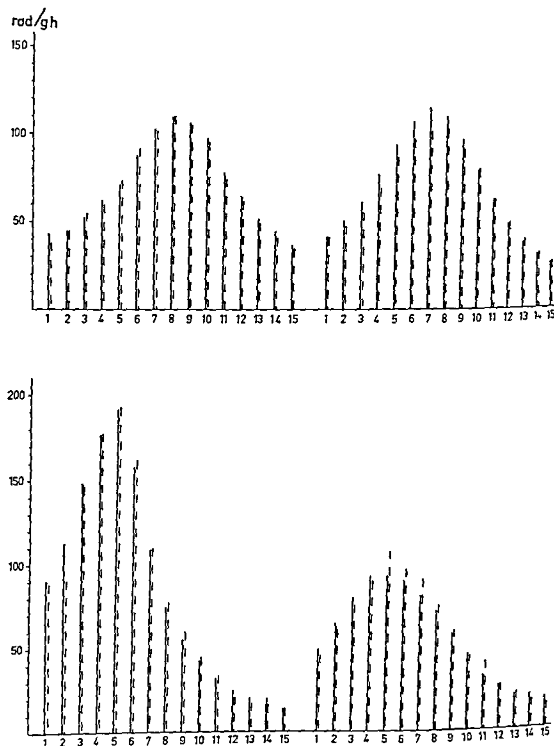


Fig 5 Dose rates per gram radium (ordinate) plotted against the serial number of the dosimeters (abscissa) Case 4 (upper diagram) represents symmetric conditions the dotted lines correspond to the second measurement Case 6 (lower diagram) is asymmetric

Table 2

Total dose in rad including the radium treatment and the subsequent external therapy with 5 MV roentgen in Case 4

Dosimeter No.	Dose contribution in rad					
	Left			Right		
	Ra	5 MV	Total	Ra	5 MV	Total
1	200	467	667	208	1400	1608
2	225	597	822	246	3547	3793
3	268	2502	2770	294	4518	4812
4	304	3491	3795	369	4462	4831
5	362	3697	4059	455	4275	4730
6	450	3697	4147	524	4089	4613
7	513	3585	4098	546	3921	4467
8	550	3454	4004	537	3790	4327
9	529	3379	3908	474	3790	4264
10	485	3678	4163	400	3883	4283
11	381	3566	3947	315	4070	4385
12	317	3603	3920	246	4014	4260
13	253	3846	4099	192	3995	4187
14	232	3921	4134	157	3977	4134
15	179	4145	4324	129	3921	4050

Dosimeters with the same number are not necessarily located in the same transverse plane on the left and right sides.

10 minutes at 100 °C prior to each read-out as suggested by ZIMMERMAN et coll. (1966). This procedure makes the calibration factors independent of the time lag between exposure and reading provided it does not exceed a few days. The heating is not sufficient however for stabilizing the sensitivity of the dosimeters. By planning the measurements so that the dosimeters were exposed within 200 rad the change in sensitivity was slow.

The calibration values for three dosimeters chosen at random are presented in Fig. 3. The straight lines were calculated according to the method of least squares. The standard deviation amounts to ± 3 %. The response increased by about 50 % between the first and second exposures but after the third exposure the dosimeters became more stable with only a minor increase in sensitivity of about 0.5 % between successive measurements. The cumulated response of the 15 dosimeters in one special probe is also given in Fig. 3.

The ability to reproduce the dose given in the calibration procedure is better

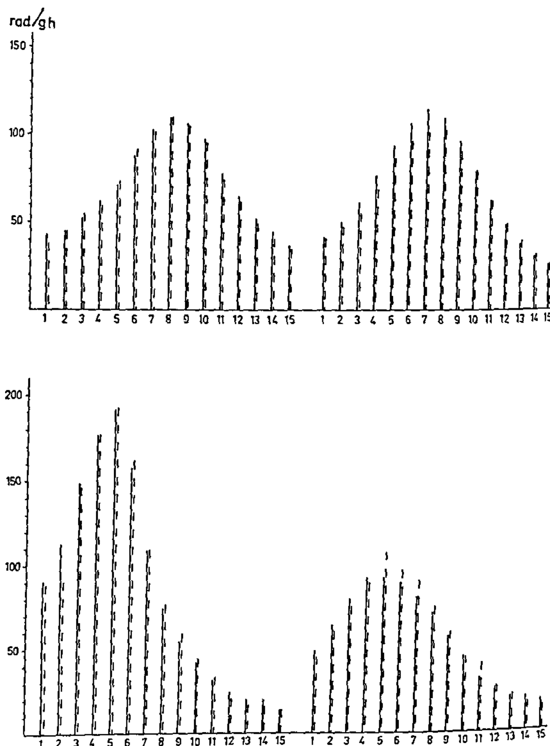


Fig 5 Dose rates per gram radium (ordinate) plotted against the serial number of the dosimeters (abscissa) Case 4 (upper diagram) represents symmetric conditions the dotted lines correspond to the second measurement Case 6 (lower diagram) is asymmetric

Table 4

Comparison between calculated and measured doses expressed in rad p r gramhour in Case 6

Dosimeter No	Left side		Right side	
	Calculated dose	Measured dose	Calculated dose	Measured dose
1	—	90 6	—	49 6
2	—	113 2	—	64 8
3	148 6	148 8	—	80 3
4	174 3	177 2	—	9? 5
	188 6	191 6	95 7	92 8
6	147 1	158 2	91 4	90 2
7	110 0	109 1	80 0	80 9
8	76 4	74 8	65 7	71 3
9	55 0	55 0	57 1	57 5
10	4? 1	42 8	41 4	45 5
11	3? 1	31 9	30 7	3? 2
1?	?4 3	24 8	23 6	26 0
13	—	20 ?	1? 9	20 0
14	—	20 1	—	19 8
1	—	13 5	—	17 ?

Table 5

Maximum dose values in rad per gramhour measured during the radium treatmen — Points of maximum doses are not specified and are not the same in the different cases

Case	Left side	Right side
1	113	85
	107	73
2	1?8	153
3	1?9	96
	89	89
4	110	111
	110	104
5	117	105
	115	105
6	192	93
	193	107

Maximum value 193 rad per gramhour minimum value 73 rad per gramhour mean value 115 rad per gramhour

Table 3

Total dose in rad including the radium treatment and the subsequent external therapy with 5 MV roentgen in Case 6

Dosimeter No	Dose contribution in rad					
	Left			Right		
	Ra	5 MV	Total	Ra	5 MV	Total
1	422	4089	4511	224	3995	4219
2	532	3901	4431	295	3846	4141
3	694	3790	4484	367	3827	4194
4	833	3659	4492	428	3529	3957
5	904	3566	4470	470	3473	3943
6	752	3678	4430	439	3398	3837
7	514	3883	4397	404	3715	4119
8	357	3846	4203	344	3827	4171
9	269	3771	4040	276	3790	4066
10	205	3753	3958	211	3809	4020
11	154	3715	3869	172	3734	3906
12	107	3585	3692	124	3659	3783
13	87	3099	3186	98	2091	2189
14	85	728	813	85	616	701
15	64	541	605	73	485	558

Dosimeters with the same number are not necessarily located in the same transverse plane on the left and right sides.

than 0.5 % and the absolute error of the calibration factor of the source is 2 % so that the maximum error in these measurements appears to amount to ± 6 %.

Results and Discussion

The absorbed doses were measured at 30 points, 15 points on each side of the midline in a single measurement. It is of little use presenting all the 330 values in the eleven measurements. Four points of reference have been chosen viz. those where the iliac veins cross the transverse planes through the principal obturator nodes and the hypogastric nodes. These points lie close to the main pathways of lymphatic spread and may, in the authors' opinion, be regarded as key points of reference for the assessment of optimal radiation doses. The planes are indicated in Fig. 1.

The main results are presented in Fig. 4, in which the dose rates per gram radium at the specified points have been plotted and the standard deviations and mean values are included. There is a slight difference between the left and right

SUMMARY

Cylindric LiF teflon rods were used as thermoluminescence dosimeters for measuring doses at thirty points inside the iliac and caval veins bilaterally during the internal and external treatment of carcinoma of the cervix uteri. The results indicate that supplementary external therapy compensates for the inadequate and often asymmetric dose distribution of the internal radium treatment.

ZUSAMMENFASSUNG

Zylindrische Stäbe aus LiF Teflon wurden als Thermolumineszensdosimeter benutzt, um die Strahlendosis an 30 Stellen bilateral innerhalb der Vena cava und den Beckenvenen während Tiefenbestrahlung mit Radium und externer Röntgenbestrahlung von Cervixcarcinomen zu messen. Es wird festgestellt, dass man mit zusätzlicher externer Strahlenbehandlung die ungenügende und asymmetrische Dosisverteilung bei internen Radiumquellen kompensieren kann.

RÉSUMÉ

Les auteurs ont utilisé des baguettes cylindriques de teflon LiF comme dosimètre à thermoluminescence pour mesurer les doses en trente points à l'intérieur des veines iliaques et cave des deux cotés, au cours du traitement interne et externe du cancer du col de l'utérus. Les résultats montrent que le traitement externe complémentaire compense la distribution de dose insuffisante et asymétrique du traitement interne par le radium.

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sides In plane (1) (see Fig 1), the mean value is 84 rad per gramhour through the principal obturator nodes and 111 rad per gramhour in plane (2) through the hypogastric node plane The standard deviations ranging from 13 to 24 % indicate the topographic differences

In the ordinary radium treatment (about 6 000 mg radium hours given in 3 fractions) 504 rad will be administered in the obturator node plane and 666 rad in the hypogastric node plane KOTTMEIER (1951) reported 610 R to 2 240 R at the pelvic wall with a mean value of 1 030 R, whereas GORTON (1953) gave a range from 571 R to 1 260 R for a point near the obturator nodes, with a mean value of 860 R

In Fig 5 the dose rate per gram radium in Cases 4 and 6 are plotted against the serial number of the dosimeters The distance between two consecutive measuring points was 16 mm The symmetry in Case 4 and the asymmetry in Case 6 are in accord with the situation of the radium implant, as indicated in Figs 1 and 2 The doses cumulated to the measuring points in the same cases during radium and external treatments are presented in Tables 2 and 3 A marked asymmetry following the radium treatment, amounting to a difference of about 47 % between the left and right sides, occurred in Case 6 The difference was reduced to only 12 % when the external treatments had been added

It should be noted that the values in Tables 2 and 3 were calculated on the hypothetical basis that all the treatments were exactly reproduced

The distances in Case 6 between the dosimeters and the radium sources were estimated in the roentgenograms The dose values were calculated and compared with the measured values by using these data and our knowledge of the source strength These results are presented in Table 4 Considering the error in estimating the distances, the agreement seems fair

The maximum doses obtained during the radium treatment in all the eleven measurements were finally determined and are collected in Table 5 The points of maximum doses have not been specified in each case but they were situated between the points of reference defined above

Acknowledgements

The authors wish to express their sincere regret at the death of the former director of the gynecologic department of the centre Ass Prof Herman Leissner who together with Prof Benner initiated this work The authors also want to express their thanks to Prof Benner for advice and criticism during the completion of the work To Ass Prof B Rosengren Assoc Prof H Skoldborn and Mrs Inger Ragnhult our thanks are due for stimulating discussions and practical advice

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RECURRENT CANCER OF THE CORPUS UTERI

Clinical features and prognosis

by

SAMUEL S KUROHARA AHMED O BADIB ANTONIO A BEITIA and JOHN H WEBSTER

Although much data have been published on primary cancer of the corpus uteri relatively little information is available on the clinical features anatomical patterns of manifestation prognosis and results of management in patients who have recurrences (recurrence denotes all types of recurrence local regional and/or distant metastases) after their initial treatments (or diagnosis) One reason for this deficit is that only a few large treated groups are available and the several small series of selected cases published offer very limited information Even when data of sizable groups of patients have been published by major cancer centers the complexity of the clinical problem due to the varied clinical patterns of presentation of recurrences has posed difficulties in carrying out complete evaluation of these cases by conventional procedures

All patients with recurrent cancer of the corpus uteri treated at this center during a 21 year period were evaluated by means of computer programs designed to subdivide cases into various characteristic subgroups and to carry out statistical

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Table 1

Initial clinical and treatment variables in recurrent cancer of the corpus uteri according to histologic findings

Variables	Total	Adenoacanthoma	Adenocarcinoma	Anaplastic	Sarcoma
Number of cases	300	26	241	9	24
Mean age years	60 8	63 8	69 9	59 6	57 6
Mean recurrence years	2 58	1 88	2 97	1 33	2 71
Clinical stages					
I—1	233	22	188	6	17
I—2	25	3	19	0	3
II	17	1	16	0	0
III	21	0	14	3	4
Uterine size					
1—2 X normal	100	10	86	1	3
2—3 X	70	4	57	3	4
>3 X	30	4	18	0	8*
Uterine cavity depth					
4—8 cm	65	8	53	1	3
8—10	39	5	32	0	2
>10	7	3	3	0	1
Surgery					
Biopsy	65	10	53	2	3
Subtotal hysterectomy	55	2	46	2	5
Total hysterectomy	177	14	140	5	15
Radical hysterectomy	2	0	2	0	0
Exenteration	1	0	0	0	1
Radiotherapy					
Roentgen	23	1	20	1	1
Radium	93	11	77	1	4
Roentgen + radium	28	2	23	2	1

Significantly ($p < .05$) different from the other values not marked by * in the same horizontal row

or radiologic treatments or both before being admitted to this institute and ninety five of them were the portion of the 809 cases which had their initial treatments here The rest of the cases were those referred for management of their persistent cancers or for completion of their initial treatments or for follow up care only None of the cases were lost to follow up

Data obtained from clinical records were punched on IBM cards and analysis was carried out on the 7 040 electronic digital computer Programs designed to

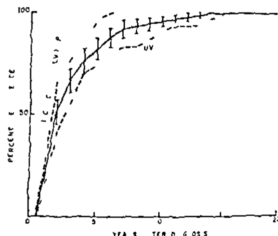


Fig 1 Percent cumulative recurrence plotted against time after diagnosis in cases of cancer of the corpus uteri Vertical bars indicate 95 % confidence intervals Curves for subgroups of cases of upper vaginal and of those with parametrial in combination with local recurrences are shown in dotted lines

analytical procedures appropriate for handling such data It has been possible to show with a certain degree of assurance (1) the anatomical patterns in which this cancer recurs in patients after initial treatment, (2) how they affect the survival of patients, and (3) how each of them may be best treated with techniques used in this series to yield the highest survival

Materials and Methods During 1945 to 1965 there were 1 109 cases registered in this institute under the diagnosis Cancer arising in the corpus uteri Three hundred of these were judged clinically to have had recurrence of their primary malignancies according to the following arbitrary criteria

1 There must have been at least a 6 month interval of complete clinical regression between initial treatment and the time of detection of recurrence

2 There must have been a minimum of two consecutive follow up examinations which failed to detect evidence of disease

3 The histologic features of the recurrent lesion, when available, must have been the same as those of the initial cancer

When tissue biopsy was not available, the occurrence of a second primary at some other site must have been clinically excluded Although biopsy was obtained in all cases of cervical corporeal or vaginal recurrences, some were not obtained in those with parametrial or internal extrapelvic metastasis Occasionally it was difficult to differentiate between recurrence and a second primary, especially in cases of internal extrapelvic cancer with the same histologic characteristics, many years after treatment for corpus cancer Since there were only two such cases, these were excluded from the study

Two hundred and five of the recurrent cases had had their primary surgical

Biopsy | Sub. hyst. | Total hyst.

Corpus Co

Cervix Cx

Upper vagina UV

Lower vagina LV

Upper and lower vagina UV LV

Upper vagina and parametria UV P

Lower vagina and parametria LV P

Upper and lower vagina and parametria UV LV P

Parametria P

Upper and lower vagina and distant or lower vagina and distant UV LV D + LV D

Upper vagina and parametria and distant or lower vagina and parametria and distant or upper and lower vagina parametria and distant UV P D+LV P D+UV LV P D

Parametria and distant P D

Distant D

Fig. 2. Scheme of anatomical patterns of recurrence in cases of adenocarcinoma or adenoacanthoma of the corpus uteri. Slash lines indicate tumor involvement. Extension beyond cervix, corpus and/or vagina in pelvis [illegible] noted as parametrial, which includes central and lateral pelvic lesions fixed or not fixed to the pelvic wall. Lateralization to the right or left is not specified. [illegible] or [illegible] or both, means both as used in Boolean logic. Arrow indicates distant spread. + means and. Few cases not specifically accounted for by scheme. [illegible] Includes three cases which had radical hysterectomy.

Table 2

Sites of initial recurrence in cancer of the corpus uteri according to histologic findings

Sites	Total	Histologic groups			
		Adenoacanthoma	Adenocarcinoma	Anaplastic	Sarcoma
Upper vagina	137	12	111	5	9
Cervix	22	1	20	1	0
Corpus	35	4	30	0	1
Lower vagina	39	6	30	0	3
Suburethra	23	3	19	0	1
Central pelvis	29	4	16**	2	7**
Lateral pelvis	90	7	64	6*	13*
Bladder	5	0	3	0	2
Rectum	5	1	3	0	1
Groin	13	0	9	2	2
Pelvic bone	4	0	3	1	0
Retroperitoneum	17	0	12	2	3
Liver	5	0	5	0	0
Stomach bowel	9	1	6	1	1
Mediastinum	1	0	1	0	0
Lung	27	2	20	2	3
Supraclavicular	3	0	3	0	0
Spine	5	1	4	0	0
Brain	2	1	1	0	0
Spinal	1	0	1	0	0

*Significantly ($p < .05$) different from the other values not marked by * in the same horizontal row.
**Significantly ($p < .05$) different from the other value marked by ** in the same horizontal row.

calculate actuarial survival rates (CUTLER & EDERER 1958) to test comparative survival and recurrence rates in sequential trials (MANTEL 1966), and to test for differences in ranked (ordered) and categorical distributions, were employed. The latter two procedures have been cited in a previous paper (KUROHARA et coll. (1969).

Results

The recurrence rate curve of the entire group of cases is shown in Fig. 1. Recurrences were detected 1/2 to 15 years post treatment. In half the number of cases, recurrence occurred within 2 years of initial treatment. Examples of curves from subgroups showing rapid and slow recurrences are also shown, i.e. subgroups with early and late recurrences. Percent cumulative recurrence is higher

Table 3 *(cont)*

Biopsy	Surgery			Radiotherapy			
	Subtot	Total	Radical	None	Roentgen	Radium	Roentgen +radium
0	17**	0	1	15 *	1	1	0
34**	0	0	0	0	1	27**	6
2	11	58**	1	51	8	10	3
3	3	25	0	15	5	6	3
4	0	12	1	4	0	11	2
3	6	12*	0	11	1	6	2
0	2	4	0	5	1	0	0
0	0	6	0	6	0	0	0
4	0	4	0	2	2	4	0
0	1	5	0	3	0	2	1
1	3	10	0	7	1	3	3
4	2	15	0	2	1	14	4
6	3	5*	0	8	0	5	1

**Significantly ($p<0.05$) different from all the other values in the same vertical column *Significantly ($p<0.05$) different from the other value marked by * in the same vertical column

of the above variables considered The scheme of 13 subgroups of anatomical patterns fractionated from 267 cases are illustrated in Fig 2 The distribution of the cases among subgroups of initial clinical and treatment variables appears in Table 3 listed in decreasing order of survival Only the major and consistent categorical differences in distribution between subgroups are indicated

Cases of lower vaginal recurrences have a lower incidence of stage I lesions than those with other patterns of recurrence at the time of the initial diagnosis All cases with cervical recurrence had an initial subtotal hysterectomy and only a few of them received radiotherapy whereas all those with corporeal recurrence had only biopsy and irradiation (Table 3) Most cases of upper vaginal or cuff lesions and a smaller number of parametrial or parametrial and distant lesions, had initial total hysterectomy

The location of recurrent lesions at single sites on the upper and lower vaginal wall respectively was as follows 22 and 11 on the anterior wall 7 and 2 on the posterior wall and 20 and 4 on either of the lateral walls In addition there were 6 with lesions encircling the vaginal lumen and 17 with apical lesions

Age and recurrence rates differ sporadically between subgroups (see Fig 6a)

Table 3

Initial clinical and treatment variables in cases of adenocarcinoma and adenoacanthoma according to patterns of recurrence

Anatomical patterns	Number of cases	Mean (years)		Stages		
		Age	Rec time	I	II	III
Cx	17	59 9	3 13	16	1	0
Co	34	62 7	2 60	31	1	2
UV	72	60 0	3 56	67	2	3
UV P	31	62 3	1 69	29	1	1
LV	17	66 4	1 71	10**	6	1
P	21	54 7	3 39	19	1	1
UV LV	6	60 8	1 33	6	0	0
LV P	6	66 0	0 93	5	1	0
UV LV P	8	66 1	1 88	6	1	1
(UV+UV LV+LV) P D	6	62 5	2 33	5	0	1
(UV LV+LV) D	14	60 1	2 17	11	1	2
D	21	59 7	2 33	19	1	1
P D	14	60 6	2 64	12	0	2

($p < 0.001$) in cases of parametrial, with or without cervical, corporeal or vaginal recurrences than in those with upper vaginal recurrences

Some of the pertinent initial clinical and treatment variables according to histologic features are recorded in Table 1 Except for the higher incidence of stage III lesions in cases of anaplastic tumor and the higher incidence of enlarged uteri in sarcoma cases, there are no differences in the material with respect to the distribution of age, recurrence rate, uterine cavity depth, initial surgery, and initial radiotherapy between histologic subgroups The data for uterine size and cavity depth were not consistently available, and are therefore incomplete

Sites of first detection of recurrences irrespective of the individual cases (some had multiple sites) are shown in Table 2 according to histologic grouping Higher incidences of lateral pelvic lesions are found in cases of anaplastic tumor or sarcoma than in those of adenocarcinoma or adenoacanthoma Cases of sarcoma have a higher incidence of central pelvic recurrence than those with adenocarcinoma No differences are found in the distributions of other sites of recurrence

Single or combinations of anatomical sites of recurrence were examined in cases of adenocarcinoma or adenoacanthoma combined, since both were similar in all

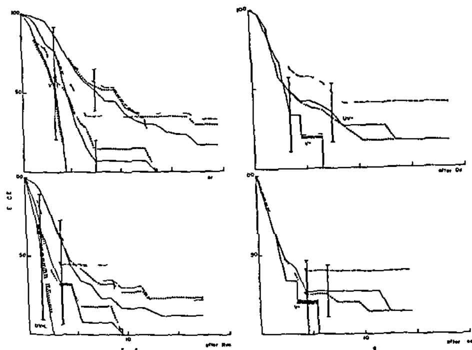


Fig 4 Survival rate curves diagnosis and after recurrence *Left diagrams* Upper vaginal (UV) lower vaginal (LV) upper and lower vaginal (UV LV) *Right diagrams* Upper vaginal and parametrial (UV P) lower vaginal and parametrial (LV P)
Curves and symbols indicated in the same manner as in fig 3

survivorship for the various anatomical subgroups The corrected survival rates are higher than the crude rates especially for the cervical and corporeal recurrence subgroups Tumor free rates are closer to the corrected ones in the above and in the upper vaginal subgroups however they are closer to the crude rates in the others This implies that patients with cancer recurrent in the cervix corpus or upper vagina have a better chance of dying free of tumor from other causes, whereas those with recurrences beyond the above sites usually die with their cancer

The results of testings of crude survival rates between subgroups are given in Fig 6 b The anatomical subgroups are arranged in prognostic order as indicated by the number of plus signs (Fig 6b) and the slopes of the curves (Figs 3 to 5) Probably due to the limitations in sample size only three statistically distinct prognostic anatomical subgroups were found Cases of cervical corporeal or upper vaginal recurrences have the highest survival those with lower vaginal or parametrial alone or parametrial in combination with other local sites have

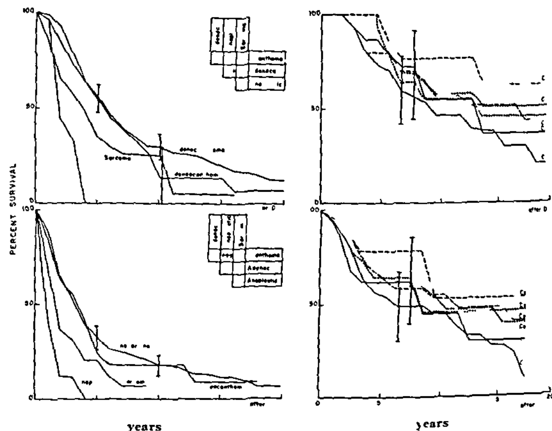


Fig 3 Survival rate curves after diagnosis and after recurrence *Left diagrams* Histology significance levels (+ to + + +) for test between subgroups referred to in fig 6 *Right diagrams* Cervical (Cx) and corporeal (Co)

Crude survival rate curves are shown in solid lines those corrected for other causes of death in dashed lines and tumor free survival curves in dotted lines vertical bars indicate 95 confidence intervals Alphameric abbreviations of anatomical patterns are referred to fig 2 and curve-testing results to fig 6

however it is seen in Table 3 that the mean recurrence time is consistently lower in those with lower vaginal upper and lower vaginal recurrences

Crude actuarial survival rates, survival rates corrected for deaths due to intercurrent disease and tumor free survival rates after time of diagnosis or of recurrence were calculated to evaluate prognosis The crude survival curves for the histologic subgroups and all three types for the various anatomical subgroups are presented in Figs 3– 5 Survival after diagnosis or recurrence is poorer for the anaplastic carcinoma subgroup than for the adenoacanthoma and adenocarcinoma It is also poorer for the sarcoma than for the adenocarcinoma

Despite the fact that specific causes of death were unknown in 57 of 242 cases and tumor status in 16 and that these indeterminate cases were considered as failures interesting trends are observed in the relationship of the three types of

	C	UV	UV+P	LV	P	UV LV	LV P	UV+LV+P	(UV UV LV+LV) P D	(UV LV +LV)+D	D	P D	A atomi l P
				+				+					C
					+								C
D								+					UV
(UV LV LV) D					+ +		+ +						UV P
(UV+UV+LV+LV)+P+D													LV
UV LV P							+	+ +					P
LV P													UV LV
U LV													LV P
P											+		UV LV P
LV													(UV+UV LV LV)+P+D
UV P						+		+					(UV LV+LV) D
UV						+			+	+ +			D
Ce													
C						+ +				+			
Anatom cal Patter	9 D	D	(UV LV +LV)+D	(UV+UV LV+LV +P D	UV+LV+P	LV P	UV LV	P	LV	UV P	UV	C	

a

	Ce	UV	UV+P	LV	P	UV LV	LV P	UV+LV+P	(UV+UV +LV+LV) D	UV LV +LV)+D	D	P D	A mic l Patt rn
				+ +	+ +	+++	+	+ +	+ +	+ +	+ +	+++	C
			+	+ +	+ +	+ +	+	+ +	+ +	+ +	+++	+++	C
D				+++	+ +	+++	+	+ +	+ +	+ +	+++	++++	UV
(UV LV+LV) D												+	UV P
(UV+UV LV LV)+P+D													LV
UV L P													P
LV P													UV LV
UV LV	+												LV P
P	+			+									UV LV P
L	+++			+									(UV+UV LV+LV)+P+D
U P	++			+									(UV LV+LV) D
U	++ +	+	+++	+	++	+	++	++	+ +				D
Ce	+ +	++	+ +	+ +	++	+	+++	++	+ +	+			
C	+	+++	+ +	+	++	+		+++	+ +				
Anatom l Pa	P D	D	(UV LV +L)+D	(UV+U +LV LV) P D	UV+LV+P	L	UV L	P	LV	UV P	UV	C	

b

Fig 6 Tabulation of significance levels obtained from tests between anatomical subgroups of rank distribution of variables in cases of recurrent adenocarcinoma or adenoacanthoma of the corpus uteri *Upper diagram* Levels for age (right upper off-diagonal blocks) and for recurrence rates (left lower blocks) Mean values for age at diagnosis and for time to recurrence are shown in Table 3 *Lower diagram* Levels for crude survival rates after diagnosis (right upper off-diagonal blocks) and after recurrence (left lower blocks) Survival curves are shown in figs 3—5 + indicates $p \leqslant 0.05$ ++ $p \leqslant 0.01$ +++ indicates $p \leqslant 0.005$ and ++++ $p \leqslant 0.001$ Alphameric notations are referred to fig 2 Legend continued on p 387

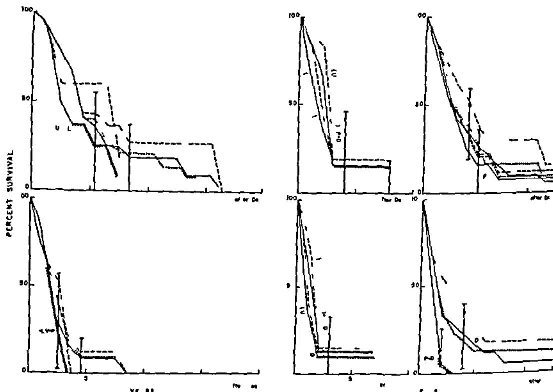


Fig 5 Survival rate curves after diagnosis and after recurrence *Left diagrams* Parametrial (P) upper and lower vaginal and parametrial (UV LV P) *Middle diagrams* Distant in combination with upper and lower vaginal and/or lower vaginal (UV LV+LV) D parametrial and distant in combination with upper vaginal upper and lower vaginal and/or lower vaginal (UV+UV LV+LV) P D *Right diagrams* Distant (D) or parametrial and distant (P D)

Curves and symbols indicated in the same manner as in fig 3

middle, and those with distant lesions alone, or in combination with other sites the lowest (Fig 7, left diagrams) Fewer cases in the best prognostic subgroup had total hysterectomy, and fewer in the worst subgroup biopsy and radiotherapy Recurrence rate was higher in the middle subgroup than in the others The distribution of cases for the other variables was uniform

Because of the fairly long time interval during which these cases were collected, survival rates of the three major subgroups were calculated after dividing each of them into cases admitted before 1956 and those admitted during or after that year (Fig 7 right diagrams) Except for the distant recurrence subgroup the other two are prognostically homogenous with respect to admission time

Contin legend of Fig 6

As an example age distributions of cases with recurrence in the lower vagina is significantly different from those with recurrence in the cervix The direction of this difference is indicated by the mean values found in Table 3

Fig 7 Statistically distinct prognostic anatomical subgroups in cases with recurrent adenocarcinoma or adenoacanthoma of the corpus uteri *Left diagrams* Crude survival rate curves for all vaginal cervical or corporeal recurrences for the parametrial recurrences with or without local lesions and for the distant recurrences with or without parametrial and/or local lesions (refer to figs 2 and 3) *Right diagrams* Crude survival rate curves of the three subgroups in cases admitted before 1955 (solid lines) and after 1955 (dotted lines)

and more with massive local recurrence and poorer survivals in both subgroups than in the combined adenocarcinoma and adenoacanthoma subgroup No remarkable differences were found in the distribution of cases between subgroups for the other variables

The cumulative recurrence curve for the adenocarcinoma and the adenoacanthoma subgroup is nearly identical to that of another large experience (LINDGREN 1957) Other centers have published some data on a small number of selected cases usually vaginal recurrent cases indicating that 69 to 84 percent of their recurrences are detected between two to three years after diagnosis (FINN 1950 IREM 1958 PRICE et coll 1965 RUBIN et coll 1963 SPEERT 1949) The type of initial treatment (total hysterectomy total hysterectomy and preoperative irradiation subtotal hysterectomy subtotal hysterectomy and pre or post-opera

intervals Part of the reason for the lower survival after recurrence in the distant recurrence subgroup admitted after 1955 than in that subgroup admitted prior to 1956, was the higher incidence of cases with lung metastasis in the latter period

The relationship between recurrence time and survival is presented in Fig 8, a to c, and the survival rates following initial treatment in Fig 8 d There is a direct (significantly linear) relationship between recurrence time and survival time after diagnosis, whereas none is seen with reference to survival time after recurrence The former relationship is usually found to be the case because survival time after diagnosis is dependent on recurrence time The latter relationship may or may not be direct because both variables are independent of each other Although the relationship between recurrence time and survival time after recurrence is not linear, survival rate curve after recurrence in cases with a long time to recurrence interval (over 5 years) is much higher than that in cases with a short interval (1—2 years) The curve for cases with an intermediate time to recurrence interval lies between the above two curves After 6 or 7 years survival post recurrence, the curves for cases with long and middle intervals become identical Part of this effect is due to the increasing incidence of deaths unrelated to the endometrial cancer

Survival after diagnosis in cases with recurring disease was not altered by the mode of treatment employed initially when the anatomical patterns of recurrence were not considered

Discussion

Since this study was primarily concerned with recurrent cancer of the corpus uteri, the base line point of interest is taken as the time of recurrence Thus information such as the specific incidences of recurrence and the clinical and treatment factors which affect them, is not available By studying the clinical patterns of recurrence and by relating them to previous findings and treatment, to treatment for recurrence and to survival following such treatment, one can deduce information concerning the biologic nature of recurrent cancer of the corpus uteri the effects of primary and subsequent management, and indirectly, the improvement of primary treatment methods

Due to the small number of recurrent anaplastic and sarcomatous cancer cases and the heterogenous histological nature of the latter most of the following discussion will be devoted to the more homogenous histologic subgroup of the combined adenocarcinoma and adenoacanthoma cases In a brief and general summary there were more cases with advanced initial lesions in the anaplastic tumor subgroup, more with enlarged uteri initially in the sarcomatous subgroup,

recurrence elsewhere The ratio of upper to lower vaginal recurrence has been reported to be approximately 1 1 to 5 1 (BOUTSELIS et coll 1963 PRICE et coll 1965 RUTLEDGE et coll 1958) In this series this ratio is 137 62 when considering all sites and 72 17 when considering single sites The incidence of posterior wall involvement is about 10 percent (9/95) in cases with solitary vaginal recurrences and is similar to other reports (PRICE et coll RUTLEDGE et coll)

No significant differences were found between the adenocarcinoma and adenoacanthoma subgroups with respect to the other variables Histologic grading was not studied since more than half of the cases lack this evaluation

Of the numerous sites of recurrences listed in Table 2 the categorization of the cases with the above histology into the thirteen subgroups of anatomical patterns (Table 3 Fig 2) seemed reasonable Parametrial recurrence includes non fixed and fixed central or lateral pelvic tumors Distant recurrence includes all types of metastatic lesions found outside the true pelvis Further refinement of categories to take into consideration specific pelvic and distant sites resulted in a great loss of information especially since many of the cases in the distant category had multiple sites of metastasis

The major differentiating features between the anatomical subgroups are as follows (1) the somewhat lower mean age for the pure parametrial subgroup (2) the somewhat shorter mean recurrence time for the lower vaginal and parametrial (3) the more advanced initial clinical stage for the lower vaginal subgroup (4) the common primary treatment of subtotal hysterectomy in the cervical subgroup and of biopsy and irradiation in the corporeal subgroup (5) the more frequent use of total hysterectomy without irradiation in the upper vaginal subgroup and (6) the less frequent use of total hysterectomy in the parametrial and parametrial and distant subgroups

A wide variation in the overall five year survival of recurrent cases have been reported (7 to 40 percent) (RUBIN et coll 1963) Although some biologic factors in endometrial carcinoma are known to be of prognostic importance and may account for the differences in survival among the various reports *it is not clear* in a few reports whether survival was calculated from the time of initial treatment or from recurrence

Our results indicate that the anatomical pattern (location) of *recurrence is the* most important prognostic factor but this is influenced to some extent by the initial treatments and certain clinical findings Within anatomical subgroups the type of treatment administered at the time of recurrence may alter the prognosis (results presented in a subsequent paper) Exceptionally favorable survivorships are found in the cervical corporeal and upper vaginal subgroups Respective crude five year survival rates of 70 to 80 percent after diagnosis and 50 to 60 percent after recurrence may be compared to those after diagnosis for stage I

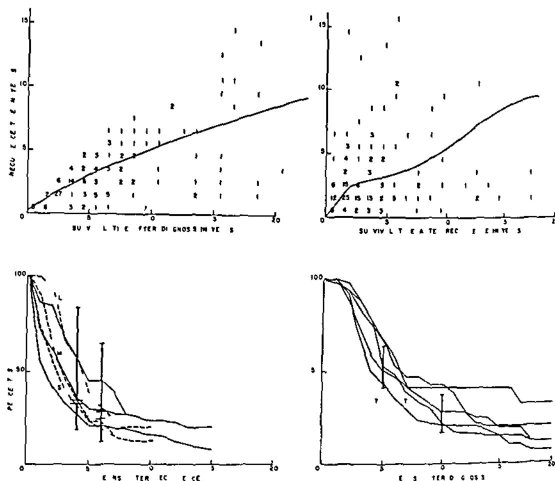


Fig 8 Relationship between recurrence time and survival in cases of adenocarcinoma or adenoacanthoma of the corpus uteri *Upper diagrams* Recurrence time plotted against survival time after diagnosis and after recurrence the number of cases falling within each yearly coordinate intervals and curves estimated by free hand drawing are shown *Lower left diagram* Crude survival rate curves after recurrence according to 1/2 to 2 year recurrence time interval (subgroup S = 172 cases) 2 to 5 year (subgroup M = 60) and over 5 years (subgroup L = 3) Solid line curve S is significantly lower than curve L ($p < 001$) Similar curves for pure vaginal recurrent cases with 57 22 and 16 cases in the respective subgroups are shown in dotted lines *Lower right diagram* Effect of initial treatments on survival of these cases crude survival rate curves after diagnosis according to initial treatment Subtotal hysterectomy (SH) 36 cases subtotal hysterectomy and radiotherapy (SH+R) 12 total hysterectomy (TH) 90 total hysterectomy and radiotherapy (TH+R) 65 and radiotherapy only (R) 59

tive irradiation in this study) did not influence recurrence rates as found elsewhere (LINDGREN) Upper vaginal recurrence occurred later than parametrial recurrences with or without local disease

The incidence of sites of recurrences are difficult to compare with those of other experiences because some authors failed to separate cases with multiple sites from those with single Vaginal recurrence has received more attention than

RÉSUMÉ

L auteur decrit les caracteristiques cliniques de 300 cas de recidive de cancer du corps de l'uterus Ce sont par ordre de gravite croissante du pronostic 241 adénocarcinomes 26 adeno-acanthomes, 24 sarcomes et 9 tumeurs anaplasiques Dans le groupe des adeno carcinomes et des adeno-acanthomes les malades atteintes de recidives cervicales cor poreales ou vaginales superieures ont eu la meilleure duree de survie celles qui avaient des recidives vaginales inférieures ou pelviennes ont eu une duree de survie intermédiaire et celles qui avaient des recidives a distant ont eu la survie la plus courte Le siege des recidives depend du type du premier traitement

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endometrial carcinoma (70 to 85 percent in most series) and after vaginal recurrence reported by others, 21 percent (PREM 1958) and 33 percent (PRICE et coll. 1965). Initial treatment was of no prognostic importance within the upper vaginal subgroup.

Prognoses of cases with *lower vaginal and with lower and upper vaginal* recurrences were as poor as those of cases with extensions of disease in the pelvis. Our observation that lower vaginal recurrence has a poorer prognosis than upper vaginal recurrences, is in agreement with those of some authors (DOBBIE 1953, PRICE et coll.) and is in keeping with the concepts of spread of endometrial carcinoma. Reverse (PREM), or no (RUBIN et coll.), effect has been reported. Nearly all cases with distant metastasis did poorly, although one survived 15 years.

There is, in general, a direct relationship between survival after recurrence and time to recurrence, but this is not clear at this time since within the total experience there are subcategories of cases with certain common features, showing inverse relationships. Work is *in progress to characterize* cases having different recurrence-survival time relationships.

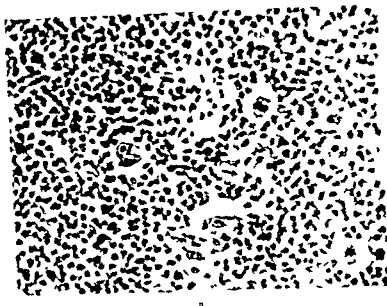
Different initial treatments, by themselves, produced no difference in survival; however, when the anatomical sites of recurrence are considered, the types of initial treatment become prognostically important because *they play some role* in determining the anatomical sites of recurrence.

SUMMARY

The clinical features of 300 cases with recurrent cancer of the corpus uteri are presented. They were in decreasing order of prognosis: 241 adenocarcinoma, 26 adenoacanthoma, 24 sarcoma, and 9 anaplastic tumor cases. *In the combined* adenocarcinoma and adenoacanthoma group, cases of cervical, corporeal or upper vaginal recurrences had the best survival, those with lower vaginal or pelvic recurrence had an intermediate, and those with distant recurrence the worst. Anatomical sites of recurrence were influenced by the type of previous treatment employed.

ZUSAMMENFASSUNG

Die klinischen Erscheinungen in 300 Rezidivfällen von Carcinomen des Corpus uteri werden vorgelegt. Diese waren in abnehmender Folge der Prognose: 241 Adenocarcinome, 26 Adenoacanthome, 24 Sarcome und 9 anaplastische Tumor-Fälle. In der Gruppe von kombinierten Carcinom-Adenoacanthomen hatten die zervikalen, korporealen und oberen vaginalen Rezidivfälle die längste Überlebenszeit, die unteren vaginalen und Becken-Rezidive hatten eine intermediäre und die distalen Rezidive hatten die kürzeste Überlebenszeit. *Der* Platz des Rezidives war von der Art der vorherigen Behandlung beeinflusst.



a



b

Fig 1 Histologic appearances in Hodgkin's disease classified according to Lukes *et coll* (1960) a) *Lymphocytic predominance* Abundant lymphocytes, some atypical reticulum cells and a Sternberg giant cell H & E

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HODGKIN'S DISEASE

Retrospective clinico-pathologic study in 149 patients

by

TORSTEN LANDBERG and LARS ERIK LARSSON

It has often been postulated in recent years that Hodgkin's disease is unicentric in origin. This together with the advent of new therapeutic methods, particularly megavoltage therapy, has led to a more optimistic view of the prognosis (CRAVER 1954, HEALY et coll. 1955, SLAUGHTER et coll. 1958, KAPLAN 1962, EASSON & RUSSEL 1963, NEWALL 1965, LASSON 1966, PETERS 1966, KAPLAN & ROSENBERG 1966, MUSSHOFF & BOUTIS 1967 and STRICKSTROCK et coll. 1967). The prognosis depends on the spread of the disease (PETERS 1950, JELLIFFE & THOMSON 1955, WESTLING 1965, and ROSENBERG 1966) and its histologic type (JACKSON & PARKER 1944, LUKES et coll. 1966). The purpose of this retrospective investigation of a material of Hodgkin's disease was to assess the significance of these two factors.

Clinical material and Methods. A total of 246 patients with Hodgkin's disease were referred for treatment during the period 1944—1960. Thirty four patients, mostly with advanced lesions, were not admitted but recommended for continuous

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Lymphocytic predominance (L p) is characterized by the occurrence of numerous lymphocytes Some histiocytes without atypia may be present On the other hand only few other inflammatory cells atypical reticulum cells and Sternberg giant cells are seen This type was originally divided by LUKES et coll (1966) into two forms a nodular and a diffuse We have tried to distinguish also these two forms and among 18 patients with lymphocytic predominance found four with the nodular form and fourteen with the diffuse form In the further analysis of the material these two forms were however pooled The type previously known as paragranuloma (JACKSON & PARKER 1944) is included under the heading of lymphocytic predominance

Nodular sclerosis (N s) is characterised by double refractive collagen connective tissue bands surrounding different sized nodular foci in the parenchyma of the lymph node These foci contain atypical reticulum cells lymphocytes leucocytes and histiocytes in varying proportions

Mixed cellularity (M c) designates the granulomatous type of Hodgkin s disease with Sternberg giant cells atypical reticulum cells inflammatory cells and fibroblasts in roughly equal proportions and irregularly intermingled with one another

Lymphocytic depletion (L d) occurs in two forms In the one reticular form there are numerous atypical reticulum cells while other inflammatory cells including lymphocytes are few This resembles a polymorphous reticulum cell sarcoma The previously known Hodgkin s sarcoma (JACKSON & PARKER 1944) belongs to this form In the other form of lymphocytic depletion there is diffuse fibrosis with a few cells of all types This probably represents a final stage Among 20 patients with lymphocytic depletion fourteen had the reticular form and six the diffuse fibrosis form

It may sometimes be difficult to classify lesions but no transitional forms were registered All the patients were assigned to those groups in which they best fitted It might be mentioned that none of the three patients in whom the histologic re-examination altered the diagnosis to non specific lymphadenitis later developed clinical signs of Hodgkin s disease furthermore of the eight patients in whom the initial biopsy strongly suggested Hodgkin s disease but in whom it could not be verified by later biopsy the further clinical course in six was typical of Hodgkin s disease The histologic types of lymphocytic predominance and nodular sclerosis were observed only in lymph nodes When other organs were involved they always had some of the other histologic characteristics

The interval between the onset of symptoms that could reasonably be assigned

treatment at their local hospitals, this left 212 patients admitted for treatment. Of these, thirty nine had previously received treatment at other hospitals, no histologic diagnosis was available in six, and eighteen patients were not accepted as having Hodgkin's disease after re-examination of the histologic preparations. In two of these latter patients no microscopic slides were available for re-examination, in three the diagnosis proved to be not Hodgkin's disease but non specific lymphadenitis, and in two patients the diagnoses were reticulum cell sarcoma and malignant systemic disease (not specified). In eleven of the eighteen patients histologic examination of biopsy specimens obtained before the beginning of treatment failed to confirm the diagnosis. This left 149 patients who had previously not been treated and in whom re-examination of lymph node biopsy specimens obtained before the beginning of treatment confirmed the diagnosis of Hodgkin's disease. These 149 patients constitute the present material.

The patients were divided according to the clinical stage of the disease at beginning of treatment (JELLIFFE & THOMSON 1955 and JELLIFFE 1965) as follows:

Stage I Lymph node involvement of only one main group, excluding intra abdominal disease.

Stage II Lymph node involvement of two or more groups in the upper or lower half of the body, excluding intra abdominal disease.

Stage III

- A Generalized lymph node involvement.
- B Intra abdominal involvement.
- C Involvement of structures other than lymphatic.
- D Constitutional symptoms for which no other reasonable cause is found.

As a rule, each patient was examined by two physicians of the department. The examination further included analysis of the blood and urine in all, roentgen examination of the lungs in 147 and cavography or urography in 11 patients. In none was lymphography before the beginning of treatment performed.

The patients were divided into various categories of forecaster index points (WESTLING 1965).

The grouping of the patients according to the histologic appearances of the initial biopsy specimens was as follows: lymphocytic predominance (L.p.), nodular sclerosis (N.s.), mixed cellularity (M.c.) and lymphocytic depletion (L.d.) (LUKES et coll. 1966) (Figs 1 to 3). The histologic re-examination of the preparations was done without knowledge of the clinical data. Only Sternberg giant cells were accepted as evidence.

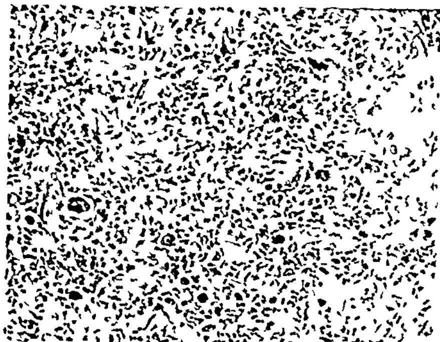


Fig 3 Histologic appearance in Hodgkin s disease classified according to LUKES et coll (1966) *Lymphocytic depletion* Diffuse fibrosis with few cells and with fragments of degenerated giant cells H & E ×160

to the disease and the beginning of treatment was taken as a measure of the previous duration of the disease

Treatment consisted mainly of radiation of the clinically involved tissues but in two patients with advanced lesions also of total body irradiation Roentgen was mostly used (170 kV 0 9 mm Cu HVL) but since 1958 also ⁶⁰Co When possible the patients were given a dose thought to be sufficient to deal with the region permanently patients with very advanced disease often received smaller doses Five patients with advanced disease and in poor general condition received no radiation Major operations had been performed in ten patients (thymectomy in one pulmectomy in one partial gastrectomy in two resection of the intestine in two splenectomy in three and decompressive laminectomy in one patient) All these ten patients received postoperative radiation Cytotoxic drugs were used mainly to relieve symptoms of advanced disease and 76 patients were treated with cytotoxics during some phase of their disease The drugs used were generally alkylating agents such as nitrogen mustard TEM and cyclophosphamide and recently vinkaleucoblastine as well Relapses were often treated at first with the same drug and when this failed another was tried Unspecific therapy with corticosteroids antibiotics and blood transfusions was used in advanced disease

The patients were regularly followed up according to the s hedule described by



a



b

Fig. 2. Histologic appearances in Hodgkin's disease classified according to LUKES et coll. (1966). a) *Mixed cellularity.* Several Sternberg giant cells in polymorphous granulation tissue with incipient interstitial fibrosis. H & E. ×160. b) *Lymphocytic depletion.* Reticular form with numerous atypical reticulum cells. H & E. ×400.

for which no other reasonable cause could be found such as marked loss of weight fatigue and itching, fever ≧ 38 C (10 patients in six of type Pel Ebstein fever) hemoglobin value of ≦ 11 g/100 ml (8 patients) leucocytes ≦ 4 000/ml (3 patients) and ESR more than 100 ml/hour (6 patients) In all the twelve patients there were three or more such symptoms Seven of the patients in stage I and twenty six of those in stage II had mild loss of weight fatigue sweating and itching hemoglobin value ≦ 11 g/100 ml leucocytes ≦ 4 000 ml and ESR > 25 ml/hour before the beginning of treatment The ESR was raised in twenty seven of the thirty three patients and in four it was as high as > 100 ml/hour Admission had usually been preceded by biopsy which might have influenced the evaluation of the prognostic value of the ESR The distribution of patients in stages I and II with and without constitutional symptoms was the same among the different histologic types

The clinical tage distribution according to sex and age is presented in Fig 4 The quotient males females was 14 7 for stage I 26 24 for stage II and 53 25 for stage III and the distribution of the exes among the various stages was not significantly different The patients in stage I were mean 46 7 years (median 43) at the beginning of treatment in stage II the mean was 40 4 (median 35) and in stage III the mean was 50 9 years (median 52) The difference in mean age of the patients in stages I and II (42 3 years) and patients in stage III (50 9 years) was significant

On grouping of the patients according to their histologic type of lesion the following distribution was reached

Lymphocytic predominance	18 patients	12 %
Nodular sclerosis	31 »	21 %
Mixed cellularity	80 »	54 %
Lymphocytic depletion	20 »	13 %

In the material of Lukes et coll consisting of 377 men aged 18 to 56 years the frequency of mixed cellularity was much lower (26 %) while the frequency of the other types particularly nodular sclerosis (40 %) was higher The distribution of the histologic types in men between 18 and 56 years in the present material did not differ significantly from that of the entire material In the series of Lukes et coll 75 % of the patients were between 18 and 30 years Eighteen patients of the present material were men aged 18 to 30 years In three of these the lesions were of histologic type lymphocytic predominance in six type nodular sclerosis in eight of type mixed cellularity and in one of type lymphocytic depletion This small group thus showed better agreement regarding the distribution of different histologic types with the material of Lukes et coll than did the present material as a whole Mixed cellularity was the commonest type also in a recent series of patients (Landberg & Larsson

LINDGREN (1962) The present investigation was concluded on January 1st, 1966, which means that all survivors were followed for at least 5 years 'Followed' is here understood as the time from the beginning of treatment until January 1st, 1966, or, alternatively, until death Of the 125 patients who died, forty two were examined post mortem

In the statistical analysis (Mr Leon Oxing, Department of Statistics, Lund University), differences demonstrable by the chi square test at the 5 % level were regarded as almost significant, at the 1 % level as significant, and at the 0 1 % level as highly significant

Results

Distribution of the material among different groups at the beginning of treatment The 93 men and 56 women produced a quotient of 1 7, a figure given also by JELLIFFE (1965) but higher than that in the series reported by UDDSTROMER (1934) VIDEBAEK (1950), VOUTILAINEN & SAXEN (1959) and WESTLING (1965) According to the Cancer Registry of Sweden, the quotient for 1960 was 1 4

The age distribution at the beginning of treatment indicated that the age of the men ranged from 5 to 84 years (mean 46 2, median 43) and that of the women from 16 to 92 (mean 47 8, median 50) The difference in mean age between the sexes was not significant In WESTLING's series of 250 patients the women were younger than the men, and the mean and median age of both sexes was lower than in the present material Of the 149 patients in the present material, forty seven (31 %) were 60 years or more at the beginning of treatment This figure is somewhat lower than that given by the Cancer Registry of Sweden for 1960 (39 %), but much higher than those reported by UDDSTROMER, VIDEBAEK, VOUTILAINEN & SAXEN, and by WESTLING (6 % to 14 %) Compared with certain series, the present material contained many men and aged persons

When classified according to the stage of disease, twenty one patients were assigned to stage I, fifty to stage II, and seventy eight to stage III There was thus 52 % in stage III, which is roughly the same as that in the series of JELLIFFE & THOMSON (55 %) and JELLIFFE (51 %) Sixty-six of the patients in stage III were assigned to this group because of the occurrence of one (42 patients) or more (24 patients) of the following types of involvement (A) generalized lymph node involvement (39 patients), (B) intra abdominal lymph node involvement (16 patients), and (C) involvement of structures other than lymphatic (43 patients) The remaining twelve of the 78 patients in stage III, who would otherwise have been assigned to stage I or II on clinical grounds, were allotted to stage III because of the presence of constitutional symptoms or signs

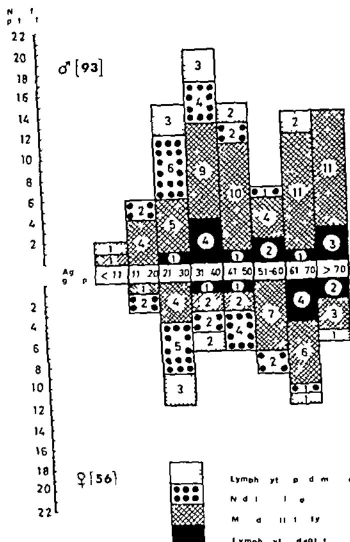


Fig 5 Age and sex distribution of patients grouped according to th histologic type of lesion The figures w thin the columns denote the number of patients

predominance was 11 7 with nodular sclerosis 15 16 with mixed cellularity 55 25 and with lymphocytic depletion 12 8 The distribution of the different histologic types did not vary significantly with sex within this material while the series of FRANSSILA et coll and KELLER et coll had a preponderance of women with nodular sclerosis compared with other histologic types

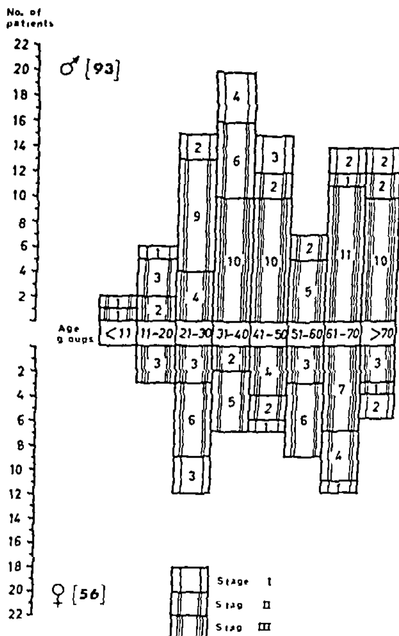


Fig 4 Age and sex distribution of the patients grouped according to the clinical stage The figures within the columns denote the number of patients

1968) although in two other retrospective investigations (Franssila et coll 1967 and Keller et coll 1968) nodular sclerosis was the commonest type

The age and sex distribution according to the histologic type of lesions are presented in Fig 5 The ratio between men and women with lymphocytic

Table 2

Patients grouped according to clinical stage and histologic type of lesion and duration of disease before beginning of treatment

History	*Histologic type*	Clinical stages I	II	III	Total
None (incidental finding)	Lymphocytic predominance	1			1
	Nodular sclerosis				
	Mixed cellularity		1	1	2
	Lymphocytic depletion				
		1	1	1	3
<6 months	Lymphocytic predominance	3	3	1	7
	Nodular sclerosis	3	11	6	20
	Mixed cellularity	6	13	24	43
	Lymphocytic depletion	1	2	10	13
		13	29	41	83
6—12 months	*Lymphocytic predominance*	*3*	*3*		6
	Nodular sclerosis		4		4
	Mixed cellularity		4	12	16
	Lymphocytic depletion	1		2	3
		4	11	14	29
12 months	Lymphocytic predominance	2	2		4
	Nodular sclerosis	1	1	5	7
	Mixed cellularity		6	13	19
	Lymphocytic depletion			4	4
		3	9	22	34

proportion between the number of patients in stage I and those in stage II did not differ significantly from one another regarding the previous duration of the disease. Of the eighteen patients with type lymphocytic predominance sixteen were distributed equally among stages I and II irrespective of the previous duration of the disease. With increasing length of history patients with nodular sclerosis and mixed cellularity tended to be relatively more often in stage III than in stages I and II. Not until after a history of more than 12 months were patients with nodular sclerosis more often in stage III than in stages I and II. Patients with mixed cellularity were almost significantly more often in stage III than in stages I and II and patients with type lymphocytic predominance independent of the duration of the disease were also most often in stage III.

Table 1

Patients grouped according to clinical stage and histologic type of lesion

Histologic type	Stage I	Stage II	Stage III	Total
Lymphocytic predominance	9	8	1	18
Nodular sclerosis	4	16	11	31
Mixed cellularity	6	24	50	80
Lymphocytic depletion	2	2	16	20
	21	50	78	149

The patients in the present material with lymphocytic predominance had a mean age of 40.3 years (median 36) at the beginning of the treatment, with nodular sclerosis the mean age was 34.4 (median 31), with mixed cellularity the mean age was 50.6 (median 54), and with lymphocytic depletion the mean age was 56.7 years (median 60). Below 45 years of age, there were 13/18 patients with lymphocytic predominance, 25/31 with nodular sclerosis, 31/80 with mixed cellularity, and 6/20 with lymphocytic depletion. This difference in age distribution of the histologic types was highly significant.

The distribution of the clinical stages among the histologic types is given in Table 1. The difference in distribution among clinical stages is most marked for the types lymphocytic predominance and lymphocytic depletion so that the former was highly significantly more common in stages I and II than lymphocytic depletion. The patients with type nodular sclerosis were significantly more often in stages I and II, while those with type mixed cellularity were significantly more common in stage III.

The previous duration of the disease was (median) 2 months for patients in stage I, 3 months for patients in stage II, and 5 months for patients in stage III. For patients with lymphocytic predominance it was 6 months, for nodular sclerosis 4 months, for mixed cellularity 5 months, and for lymphocytic depletion 4 months. LUKES et coll. found a longer duration of the disease before the initial biopsy in patients with advanced disease (staging according to PETERS 1950 and PETERS & MIDDLEMISS 1958). The duration of the disease in patients with different histologic types of lesions in the present material did not differ appreciably from the values for the duration of the disease before initial biopsy in the series reported by LUKES et coll.

A survey of the patients grouped according to clinical stage and histologic type of disease and duration of the history before beginning of treatment is presented in Table 2. Three of the patients had no symptoms. Of the patients, who had had symptoms for at the most 12 months, about half were in stage III, while two thirds of those who had had symptoms longer were in stage III. The

Table 3 *(cont.)*

Stage III					Total					At end of follow up Total				
Lp	Ns	Mc	Ld	Total	Lp	Ns	Mc	Ld	Total	Lp	Ns	Mc	Ld	Total
1	11	30	[illegible]	78	18	31	80	20	149	18	31	80	20	149
1	9	37	14	61	15	27	63	17	122	15	29	68	18	130
	5	32	11	48	6	11	43	13	73	11	23	59	15	108
	5	15	5	25	4	20	28	5	57	9	23	41	8	81
	3	25	9	37		3	28	9	40	4	9	37	9	59
		2	1	3			3	1	4			4	1	5
							1		1		1	1		2
	1	13	2	16		1	13	2	16	3	10	31	4	48
												1		1
												1		1
	1			1		1			1		1			1
	1	12	3	16		1	12	3	16	2	8	22	4	36
			1	1				1	1				1	1
											2			2
											2	4		6
	1			1		1			1	1	1	3		5
		6	3	9			6	3	9	6	4	19	4	33
	1	5	4	10		1	5	4	10	3	5	13	5	26
		3	1	4			3	1	4	1	1	4	1	7
											1	1		2
	2	1		3		2	1		3		8	10	1	19
	3	5	1	9		3	5	1	9		5	6	1	12
											3	1		4
											1			1

LING's fifty had 0 or 1 point, thirty five had 2 points and fifty six patients had 3 or more points. Eight patients could not be classified, not even with substitution. The distribution among different categories of forecaster index points agrees largely with that in WESTLING's series, with minor differences, which were not significant.

Clinical manifestations and autopsy findings in patients with different histologic types of lesions. In Table 3 the number of patients in different clinical

Table 3

Patients grouped according to clinical stage, histologic type of lesion and clinical involvement at the beginning of treatment and present or previously treated lesions at the end of follow-up.—L. p. designates lymphocytic predominance, N. s. nodular sclerosis, M. c. mixed cellularity and L. d. lymphocytic depletion

	At beginning of treatment									
	Stage I					Stage II				
Histologic type	L. p.	N. s.	M. c.	L. d.	Total	L. p.	N. s.	M. c.	L. d.	Total
Total number of patients	9	4	6	2	21	8	16	24	2	50
Lymph nodes in neck and s. clav. fossa	6	2	4	1	13	8	16	22	2	48
Lymph nodes in axilla	3	1	1	1	6	3	5	10	1	19
Lymph nodes in mediastinum		1			1	4	14	13		31
Lymph nodes in groin			1		1			2		[illegible]
Lymph nodes in cubital or *popliteal fossa*								1		1
Waldeyer's tonsillar ring								1		1
Lymph nodes in abdomen										
Maxilla										
Orbita										
Thymus										
Pulm. parenchyma										
Oesophagus										
Pericard. pleura										
Thoracic wall										
Breast										
Liver										
Spleen										
Other abd. viscera										
Perineum rectum										
Skeleton										
Skin										
Spinal canal										
Thigh muscle										

If, then, the interval between the initial symptoms and the beginning of treatment be taken as a measure of the duration of the disease, a long duration may explain advanced disease in some patients though the histologic type lymphocytic depletion had spread rapidly. However, in patients with lymphocytic predominance, despite a longer duration of the disease, this was rarely generalized at the beginning of treatment. Nodular sclerosis appeared to have spread slower than mixed cellularity.

When classifying the patients according to forecaster index points (WEST-

Table 3 *(cont)*

Stage III					Total					At end of follow up Total				
Lp	Ns	Mc	Ld	Total	Lp	Ns	Mc	Ld	Total	Lp	Ns	Mc	Ld	Total
I	11	50	16	78	18	31	80	20	149	18	31	80	20	149
1	9	37	14	61	15	27	63	17	127?	15	29	68	18	130
	5	3?	11	48	6	11	43	13	73	11	23	59	15	108
	5	15	5	25	4	20	28	5	57	9	23	41	8	81
	3	25	9	37		3	28	9	40	4	9	37	9	59
		?	1	3			3	1	4			4	1	5
							1		1		1	1		2
	1	13	7	16		1	13	2	16	3	10	31	4	48
												1		1
												1		1
	1			1		1			1		1			1
	1	12	3	16		1	12	3	16	2	8	22	4	36
			1	1				1	1				1	1
											2			2
											2	4		6
	1			1		1			1	1	1	3		5
		(	3	9			6	3	9	6	4	19	4	33
	1	5	4	10		1	5	4	10	3	5	13	5	26
		3	1	4			3	1	4	1	1	4	1	7
											1	1		2
	?	1		3		2	1		3		8	10	1	19
	3		1	9		3	5	1	9		5	6	1	12
											3	1		4
											1			1

LING fifty had 0 or 1 point thirty five had 2 points and fifty six patients had 3 or more points Eight patients could not be classified not even with substitution The distribution among different categories of forecaster index points agrees largely with that in WESTLING s series with minor differences which were not significant

Clinical manifestations and autopsy findings in patients with different histologic types of lesions In Table 3 the number of patients in different clinical

Table 4

Patients grouped according to histologic type of lesion and stage at the beginning of treatment and histologic type and localization of the disease at autopsy L p = lymphocytic predominance N s = nodular sclerosis M c = mixed cellularity, L d = lymphocytic depletion Ret = reticular form of lymphocytic depletion D f = diffuse fibrosis form of lymphocytic depletion

Histologic type in initial biopsy specimen	Lympho-cytic predom inance			Nodular sclerosis			Mixed cellularity					
Patient number	47	11	95	149	93	150	1	96	30	129	152	154
Sex	♀	o	o	♂	♀	o	♀	o	o	o	♀	♀
Stage at beginning of treatment	II	II	II	II	III	III	I	I	II	II	II	II
Histologic type in autopsy specimen	*M c*	*M c*	*M c*	*D f*	*M c*	*Ret*	*M c*	*Ret*	*Ret*	*M c*	*Ret*	*Ret*
Spread of disease at autopsy												
Spleen	+	+	+	+	+	+	+	+	+	+	+	+
Liver	+	+				+		+	+	+		+
Lymph nodes in mediastinum	+	+	+		+	+		+		+		+
Lymph nodes in retroperitoneum			+	+	+	+				+	+	
Skeleton		+	+	+		+				+	+	+
Lymph nodes in axilla				+								
Lymph nodes in mesenterium						+				+		
Lymph nodes in neck and s clav fossa				+	+							
Lymph nodes in groin							+					
Kidneys								+				
Lung						+						
Pleura				+						–		
Waldeyer s tonsillar ring												
Heart												
Pericardium												
Peritoneum												
Stomach												
Small intestine												
Bladder								+				
Adrenal												
Nervous system									+			

stages and of various histologic types, with different clinical manifestations at the beginning of treatment, and present or previously treated clinical manifestations at the end of follow up are all recorded

The most common clinical findings were lymphoma of the neck or supraclavicular fossa which occurred in 122 patients (82 %) of the 149 at the beginning of treatment, and was noted at the end of the follow up in 130

Table 4 (*cont*)

													Lymphocytic depletion						Total
													Ret cular			Diffuse fibrosis			
31	44	63	66	69	77	87	88	89	9?	105	118	127	101	135	161	19	43	61	
♂	♂	o	♂	♀	♂	♂	♀	♂	o	o	♂	♂	♂	♂	♀	♀	♂	♀	
III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	III	I	III	III	
M	M	Df	M	M	M	Df	M	M	M	M	Rt	M	Rt	Df	Rt	Df	Df	Df	
+	+				+	+	+	+	+	+	+	+	+	+	+	+	+	+	28
+	+			+	+	+	+	+	+	+	+	+	+	+	+	+		+	23
+	+	+		+	+	+	+		+	+	+	+		+	+		+	+	?3
+	+		+	+	+	+			+	+	+	+	+	+	+			+	20
	+			+		+	+	+			+	+	+			+		+	17
		+		+		+	+	+		+		+			+		+		10
-								+	+	+			+	+	+			+	10
			+							+	+			+	+				7
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patients (87 %) and without any significant variation in frequency of the different histologic types

The next most common finding was lymphoma of the axilla which was present at the beginning of treatment in 73 patients (49 %) of 149 and at the end of follow up in 108 patients (73 %) The frequency of lymphoma of the axilla at the beginning of treatment was almost significantly lower in pa-

tients with lymphocytic predominance and nodular sclerosis, but at the end of follow up such a difference was no longer demonstrable

Lymphoma of the mediastinum was noted at the beginning of treatment in 57 (38 %) of the 149 patients and twenty (35 %) of these fifty seven were of the type nodular sclerosis Twenty (65 %) of the 31 patients with nodular sclerosis had at the beginning of treatment mediastinal lymphoma, compared with 37 patients (31 %) of the 118 patients with other histologic types The difference was highly significant This over representation of mediastinal lymphoma in type nodular sclerosis at the beginning of treatment was still more marked in the 71 patients with stages I and II In 32 (45 %) of these, a mediastinal lymphoma was found at the beginning of treatment and of these thirty two patients fifteen (47 %) had type nodular sclerosis In 15 (75 %) of the 20 patients with type nodular sclerosis in stages I and II, a mediastinal lymphoma was thus seen at the beginning of treatment, and this localization was highly significantly over represented among patients with nodular sclerosis compared with other histologic types (17/51 = 33 %) in stages I and II at the beginning of treatment The difference persisted significantly, so that at the end of follow up a mediastinal lymphoma was present in 18 (90 %) of the 20 patients with type nodular sclerosis in stages I and II, compared with 26 (51 %) of the 51 patients in stages I and II of the other histologic types In the entire material, mediastinal lymphoma had been noted at the end of follow up in 23 (74 %) of the 31 patients with nodular sclerosis compared with 58 (49 %) of the 118 patients with other histologic types The difference was almost significant Of the eight patients with nodular sclerosis in whom no mediastinal lymphoma was found two were in stage I and II respectively, and still had no further manifestations, while six were in stage III and died 5 to 79 months after the beginning of treatment The high frequency of mediastinal lymphoma in patients with nodular sclerosis has been stressed by LUKES et coll, FRANSSILA et coll and by KEITH et coll

Lymphoma of the groin was noted at the beginning of treatment in 40 (27 %) of the 149 patients and at the end of follow up in 59 patients (40 %) Inguinal lymphoma at the beginning of treatment was highly significantly, and at the end of follow up almost significantly, more common in patients with mixed cellularity and lymphocytic depletion than in those with lymphocytic predominance and nodular sclerosis

Retroperitoneal lymphoma had been diagnosed at the beginning of treatment in 16 (11)% of the 149 patients and at the end of follow up in 48 (32 %) The frequency was almost significantly higher for patients with mixed cellularity It is known (LEE et coll 1964) that cavo urography, and particularly lymphography may often reveal asymptomatic retroperitoneal lymphoma The

low frequency of diagnosed retroperitoneal lymphomas in the present material at the beginning of treatment can probably be explained by the fact that cavo urography was not performed so often and that lymphography was not performed at all The figures must therefore be regarded as reflecting only the frequency of symptomatic retroperitoneal lymphomas Still lower figures have been given by WESTLING and by MUSSHOFF et coll (1966)

Involvement of the lymph nodes in the cubital or popliteal fossa was present at the beginning of treatment in four and involvement of one of the tonsils in one patient

Tissues other than the above mentioned lymph node groups were found to be affected at the beginning of treatment in 43 (29 %) of the 149 patients and at the end of follow up in 90 patients (69 %) Such involvement both at the beginning of treatment and at the end of follow up was almost significantly equally common among patients with nodular sclerosis mixed cellularity and lymphocytic depletion but at the beginning of treatment it was significantly and at the end of follow up almost significantly less common among patients with lymphocytic predominance Involvement of the skeleton spinal canal and of the skin was somewhat more common among patients with nodular sclerosis FRANSSILA et coll reported involvement of the skeleton to be more common in nodular sclerosis The pulmonary parenchyma the liver and the spleen were somewhat more often affected by mixed cellularity and lymphocytic depletion at the beginning of treatment not later The difference regarding the pulmonary parenchyma was significant

Involvement of abdominal organs (e g lymph nodes liver spleen stomach) was present at the beginning of treatment in one (2 %) of the 49 patients with lymphocytic predominance and nodular sclerosis compared with 27 (27 %) of the 100 patients with mixed cellularity and lymphocytic depletion The difference was highly significant No such difference was however demonstrable at the end of follow up

The follow up period for patients with lymphocytic predominance had a median of 60 months (mean 70) for nodular sclerosis the median was 63 (mean [illegible]) for mixed cellularity it was 15 (mean 32) and for lymphocytic depletion it was 5 months (mean 13) At the end of the follow up six of the patients with lymphocytic predominance ten with nodular sclerosis seven with mixed cellularity and one with lymphocytic depletion were still alive

Judging from the varying duration of the follow up of the patients with different histologic types of disease mixed cellularity and particularly lymphocytic depletion appear to run a faster course than lymphocytic predominance and nodular sclerosis

Evaluable autopsy specimens were available for thirty-one of the patients The

Table 5

Histologic type in the initial biopsy specimens and changes according to autopsy specimens in the 31 patients in this group

Histologic type at initial biopsy		Histologic type in autopsy specimen				
		Lymphocytic predominance	Nodular sclerosis	Mixed cellularity	Lymphocytic depletion	
					Reticular	Diffuse fibrosis
Lymphocytic predominance	2	—	—	2	—	—
Nodular sclerosis	4	—	—	*2*	*1*	1
Mixed cellularity	19	—	—	12	5	2
Lymphocytic depletion						
Reticular	3	—	—	—	2	1
Diffuse fibrosis	3	—	—	—	—	3
	31			16	8	7

Table 6

Patients alive 1 to 5 years from the beginning of treatment and grouped according to clinical stage

	Total number of patients	Number of patients still alive after (years)				
		1	2	3	4	5
Stage I	21	19	16	14	13	13
Stage II	50	43	33	30	28	24
Stage III	78	27	19	11	10	7

organs or organic systems involved are given in Table 4. It is clear from the table that most of the autopsies indicated that the disease had involved the spleen, liver, mediastinal and para-aortic lymph nodes. The material would not allow closer analysis of the relation between a radiation dose to an area and its effect. It should, however, be mentioned that of the twenty-four patients treated with radiation for involvement of the lymph nodes of the neck, nineteen presented no signs of local recurrence at autopsy. The histologic type was generally the same in all organs involved in a given patient.

The distribution of the histologic types in the autopsy series was compared with the histologic types at initial biopsy (see Table 5). None of the patients who had initially had lymphocytic predominance or nodular sclerosis had such types at autopsy. A shift of the material towards prognostically less favourable

Table 7

Patients alive 1 to 5 years from the beginning of treatment grouped according to the histologic type of lesion

Histologic type	Total number of patients	Number of patients alive after (years)				
		1	2	3	4	5
Lymphocytic predominance	18	16	13	11	10	9
Nodular sclerosis	31	28	22	21	19	17
Mixed cellularity	80	41	31	21	20	17
Lymphocytic depletion	20	4	2	2	2	1

histologic types had occurred an observation in agreement with previous investigations that the disease can change in character also as regards its histologic type (HANSON 1964 and LOHMAN 1965)

Survival in the different groups Of all the 149 patients 44 (30 %) were alive 5 years after the beginning of treatment twenty three (25 %) of the 93 men and 21 (37 %) of the 56 women The better prognosis for the women in this series which was not significant however was perhaps somewhat more distinct for stage II (men 10 26 women 14 24) and for type mixed cellularity (men 9/55 women 8 25) but none of the differences were significant SHIMKIN et coll 1955) JELLIFFE & THOMSON (1955) and FAYOS et coll (1965) reported a better prognosis for women The same tendency though not statistically demonstrable was found by PETERS (1950) PETERS & MIDDLEMISS (1958) MEIGHAN & RAMSAY (1963) and WESTLING (1965) while VIDEBAEK (1950) indicated that the prognosis was equal for both sexes

The number of surviving patients in each of the first 5 years after the beginning of treatment are given for different clinical stages in Table 6 and for different histologic types in Table 7 These values are expressed as percentages in Figs 6 and 7

The 5 year survival rate in different clinical stages (Table 6 and Fig 6) was highest in stage I and lowest in stage III The difference between stage I and stage II was not significant The 5 year survival rate in stages I and II (52 %) did not differ statistically from the corresponding figure given by JELLIFFE (58 %) Twenty-six of the thirty four patients in stages I and II who died within 5 years from the beginning of treatment bore clinical appearances of advanced Hodgkin s disease Autopsy was performed in only four of the remaining eight patients In one of these (stage II lymphocytic predominance) death was due to myocardial infarction and there was no evidence of Hodgkin s disease while in the other three (one in stage I and two in stage II all of

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Histologic type in the initial biopsy specimens and changes according to autopsy specimens in the 31 patients in this group

Histologic type at initial biopsy		Histologic type in autopsy specimen				
		Lymphocytic predominance	Nodular sclerosis	Mixed cellularity	Lymphocytic depletion	
					Reticular	Diffuse fibrosis
Lymphocytic predominance	2	—	—	2	—	—
Nodular sclerosis	4	—	—	2	1	1
Mixed cellularity	19	—	—	12	5	2
Lymphocytic depletion						
Reticular	3	—	—	—	2	1
Diffuse fibrosis	3	—	—	—	—	3
	31			16	8	7

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The number of surviving patients in each of the first 5 years after the beginning of treatment are given for different clinical stages in Table 6 and for different histologic types in Table 7. These values are expressed as percentages in Figs. 6 and 7.

The 5-year survival rate in different clinical stages (Table 6 and Fig. 6) was highest in stage I and lowest in stage III. The difference between stage I and stage II was not significant. The 5-year survival rate in stages I and II (52 %) did not differ statistically from the corresponding figure given by JELLIFFE (58 %). Twenty-six of the thirty-four patients in stages I and II who died within 5 years from the beginning of treatment bore clinical appearances of advanced Hodgkin's disease. Autopsy was performed in only four of the remaining eight patients. In one of these (stage II, lymphocytic predominance) death was due to myocardial infarction and there was no evidence of Hodgkin's disease, while in the other three (one in stage I and two in stage II, all of

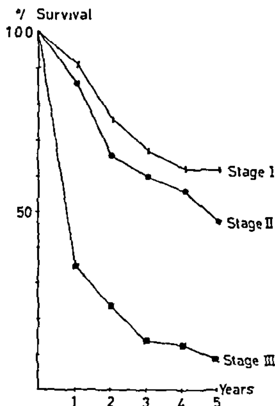


Fig 6 Survival rate of patients 1 to 5 years after the beginning of treatment grouped according to clinical stage

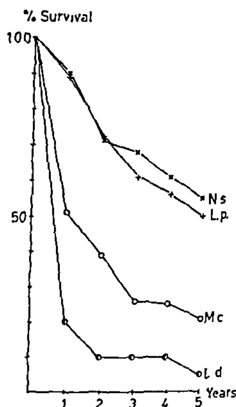


Fig 7 Survival rate of patients 1 to 5 years after the beginning of treatment grouped according to the histologic type of lesion

mixed cellularity type) Hodgkin's disease was demonstrated at autopsy One patient (stage I lymphocytic predominance) also had a soft tissue sarcoma with metastases and advanced carcinoma of the thyroid Autopsy was not performed but the clinical course was at least compatible with Hodgkin's disease Three patients (one in stage I and two in stage II one with lymphocytic predominance and two with mixed cellularity) died at home and were lost to control

Of the thirty three patients in stages I and II who had one or two constitutional symptoms at the beginning of treatment, fifteen (45 %) were alive 5 years after the beginning of treatment compared with twenty two (58 %) of the thirty eight of those in whom such symptoms had not been demonstrated The difference was not significant

In all the seventy one patients in stage III who died within 5 year after the beginning of treatment the clinical picture at death was that of advanced Hodgkin's disease Of the seven patients in stage III who survived 5 years after the beginning of treatment three had nodular sclerosis and four had mixed

Table 8

Number of patients ali e 5 years after the beginning of treatment and total number of patients grouped according to clinical sta e and histologic type of lesion at the beginning of treatment

Histolog c type	Stage I	St ge II	Stage III	
Lymphocytic predom nance	7/9	2/8	0 1	9/18
Nodular scle os s	4 4	10 16	3/11	17/31
Mi xed cellular ty	2/6	11/74	4/50	17/80
Lymph cyt c deplet on	0 2	1/	0/10	1/20
	13/21	24 50	7/ 8	44 149

Table 9

Fi e year survivals in different categories of forecaster index po nts (after WESTLING 1965)

Number of forec ster index points	Total number of patients	Number of patients alive 5 years after beginning of tre tment
0 or 1	50	28
2	35	9 1
3 or more	56	2
Not clas ifiable	8	5

cellularity The reason why these seven patients were classified as stage III was that two had only generalized lymph node involvement two had generalized lymph node involvement plus involvement of structures other than lymphatics (pulmonary parenchyma and liver) and three had involvement of structures other than lymphatics (pulmonary parenchyma skeleton and skin respectively) The difficulty in the evaluation of skin changes has been stressed by JELLIFFE Of the twenty eight patients classified as stage III because of generalized lymph node involvement and or involvement of retroperitoneal lymph nodes two were alive 5 years from the beginning of treatment and the 5 year survival rate for this group was thus no better than for the other patients in stage III

The 5 year survival rate for different histologic types is given in Table 7 and Fig 7 It was the same for lymphocytic predominance and nodular sclerosis but highly significantly worse for mixed cellularity and worst for lymphocytic deple tion LUKES et coll reported a longer median survival for types lymphocytic pre dominance and nodular sclerosis than for types mixed cellularity and lympho cytic depletion and especially large differences between the nodular form of lymphocytic predominance and the diffuse fibrosis form of lymphocytic deple tion All the four patients of the present material with nodular lymphocytic pre

dominance were alive 5 years from the beginning of treatment, while of the six with diffuse fibrosis all had died within 5 years. FRANSSILA et coll. gave similar figures for the 5 year survival. The series reported by KELLER et coll. is not comparable because of differences in the therapeutic technique.

The 5 year survival in different clinical stages was distributed among different histologic types as seen in Table 8. The possibility of a 5 year survival seems to depend both on the clinical stage at the beginning of treatment and on the histologic type of lesion. Of thirteen patients with types lymphocytic predominance and nodular sclerosis stage I, eleven (85 %) were still alive after 5 years and of the thirty seven patients with types lymphocytic predominance and nodular sclerosis in stages I and II, twenty three (62 %) were alive after 5 years. The corresponding figure for patients in stage III of types mixed cellularity and lymphocytic depletion was four (6 %) out of sixty six patients. As previously mentioned, in eight of the thirty four patients in stages I and II who died within 5 years the cause of death could not with certainty be classified as advanced Hodgkin's disease. Three of these had lymphocytic predominance and five had mixed cellularity.

The 5 year survival in different categories of forecaster index points (WESTLING 1965) is presented in Table 9. Five of the eight patients who could not be classified were still alive at 5 years, which might help to explain why the 5 year survival rate was lower for all the three categories in the present material than in WESTLING's. The differences were not significant, however.

SUMMARY

A retrospective study of 149 patients with Hodgkin's disease indicated that the further course from the beginning of treatment depended both on the clinical stage and the histologic type of the initial biopsy specimen. The clinical staging and a differentiated histologic evaluation appear to be important in the evaluation of the prognosis of the disease.

ZUSAMMENFASSUNG

Eine retrospektive Analyse von 149 Patienten mit Hodgkins Erkrankung zeigte, dass der weitere Verlauf nach Beginn der Behandlung sowohl vom klinischen Stadium der Erkrankung als auch vom histologischen Typ der ersten Probeexcision abhing. Es ist demgemäss wichtig, für die Prognose das klinische Stadium und den histologischen Typ bei Anfang der Behandlung richtig einzuschätzen.

RÉSUMÉ

L'étude rétrospective de 149 malades atteints de maladie de Hodgkin montre que l'évolution à partir du début du traitement dépend à la fois du stade clinique et du type histologique du prélèvement biopsique initial. Il semble que la définition du stade clinique et l'établissement d'un diagnostic histologique différencié sont importants pour établir le pronostic de la maladie.

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FROM THE RADIOTHERAPY CLINIC (DIRECTOR PROF L R HOLSTI) UNIVERSITY CENTRAL HOSPITAL, HELSINKI FINLAND

PREGNANCY FOLLOWING TREATMENT OF MAMMARY CARCINOMA

by

PENTTI M RISSANEN

Carcinoma of the female breast is most common after the menopause Fewer than 15 per cent of mammary carcinomas appear to develop during the child bearing period (DONEGAN 1967) and pregnancies following their treatment are consequently relatively rare It is possible that patients with far advanced mammary carcinoma fail to become pregnant because of the disease alone Most of the materials published comprise some twenty or thirty cases (HARRINGTON 1937 WESTBERG 1946 ADAIR 1953 PETERS 1962) WHITE (1954) collected 196 cases from the literature and added 12 of his own When pregnancy occurs after treatment for mammary carcinoma the main points of interest are whether and how the pregnancy and the time at which it occurs affect the disease treated earlier and whether or not they affect the prognosis Moreover the advisability of interrupting the pregnancy must be considered and the attitude to be adopted towards ovariectomy should be given careful thought

Material and Methods The series comprises 53 patients with mammary carcinoma treated in the period 1936—1959 The patients had become pregnant once or more often after primary therapy The youngest of the patients was 21

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Table 1

Therapeutic methods employed for primary tumours in different stages

	Stages		
	I	II	III
Local excision and postoperative radiotherapy	3	—	—
Simple mastectomy and postoperative radiotherapy	1	—	—
Radical mastectomy and postoperative radiotherapy	19	14	4
Radical mastectomy and pre and postoperative radiotherapy	5	6	1

the oldest 44, the mean age being 34 years Four of the patients had been treated for mammary carcinoma during an earlier pregnancy 3 to 24 years earlier The first symptom had been an axillary lump in one patient and a lump in the breast in all the others The duration of the symptoms prior to admission was one week to two years average about 3 1/2 months Twenty three of the tumours were in the right and thirty in the left breast The tumour was localized in the lateral half of the mammary gland in twenty nine in the medial half in eleven, and centrally in two patients The exact localization was not known in eleven instances

The primary tumours established and treated were divided into groups according to the TNM system The clinical staging was as follows 28 cases in stage I, 20 cases in stage II, 5 cases in stage III, and none in stage IV

Approximately 91 % of the cases were carcinomas in stages I and II Metastases in the axillary lymph nodes were on admission diagnosed in 23 of the cases (43 %) The distribution according to the histologic diagnoses was as follows

Adenomatous carcinoma	22
Solid carcinoma	12
Scirrhous carcinoma	6
Colloid carcinoma	1
Carcinoma (not otherwise specified)	12

Division into different grades of malignancy from the histologic appearances was omitted

The primary tumours were usually treated by radical mastectomy followed by radiotherapy The other methods are listed in Table 1 Both pre and postoperative radiotherapy consisted of roentgen irradiation mostly with factors of

Table 2

Pregnancies following treatment of patients with mammary carcinoma in different stages

	Stages		
	I	II	III
One pregnancy	16	15	4
Two pregnancies	11	4	1
Three pregnancies	1	1	–

Table 3

Number of pregnancies abortions and deliveries in patients with tumour in different stages

	Stages			Total
	I	II	III	
Abortion	11	13	2	26
Delivery	30	13	4	47
Total	41	26	6	73

180 to 250 kV 10 to 15 mA 0 5 mm Cu FSD 50 cm to the area of the breast the supraclavicular fossa and axilla The skin dosage was 1 400 to 2 800 R After the primary treatment of carcinoma of the breast six patients developed metastases in the lymph nodes or skin before the start of pregnancy for which they were treated (one in stage I four in stage II and one in stage III)

The number of pregnancies from one to three after the primary treatment for mammary carcinoma are given in Table 2 In the 53 patients in the present series a total of 73 pregnancies occurred during the follow up period In 26 instances the patients underwent termination of pregnancy or had a spontaneous abortion and in 47 instances the pregnancy ended with delivery

The distribution of deliveries and abortions in relation to the clinical stages appears in Table 3 It may be seen from Table 4 that the pregnancies in question began at different times after the primary therapy The latter table also indicates whether the pregnancies were terminated or ended with delivery

All the patients were followed up for at least 7 years from the date of admission for mammary carcinoma

Table 4

Intervals between primary therapy for mammary carcinoma and subsequent pregnancy

	<1 year	<3 years	<5 years	<10 years	>10 year	Total
Termination of pregnancy or abortion	12	9	4	1	—	26
Delivery	12	19	9	6	1	47
Total of pregnancies	24	28	13	7	1	73

Results

In the whole series, twelve patients died within 5 years of the treatment for mammary carcinoma, and the 5 year survival rate was consequently 41/53, or 77.4 %.

One of the patients (stage I) died from another disease and was free of evidence of mammary carcinoma, but all the other patients died from the condition. Of 46 patients followed up for 10 years, thirty two were alive, giving a 10 year survival rate for the total series of 32/46, or 69.5 %. The 5 year survival rates for the patients with tumours in the different clinical stages are given in Table 5; in this table the results are also analyzed according to whether the pregnancy was terminated or ended in delivery. If the patient had had several pregnancies, of which one at least had ended in delivery, she was placed in the group delivered of a baby.

As the first years following treatment for mammary carcinoma are generally regarded to be significant in deciding whether to let the pregnancy proceed or to terminate it, the cases in which pregnancy occurred during the first three years after treatment for mammary carcinoma were analyzed separately (Table 6). The different stages of the disease were not analyzed for this group.

The material included four cases in which mammary carcinoma was diagnosed during pregnancy (RISSANEN 1969). One of these, a patient with subsequent carcinoma in stage I, had three pregnancies, the first less than one year after the primary treatment for carcinoma of the breast. This and the second pregnancy were terminated but the third pregnancy ended in delivery. The patient was asymptomatic 20 years after the primary treatment. Another patient had a primary tumour in stage II. She had a normal delivery 6 years after the primary therapy and is now, 24 years later, symptom free. Two patients had a history of primary carcinoma in stage III. One of them gave birth again 16 months after primary therapy and died of mammary carcinoma 20 months later. The

Table 5

Survival rates after first pregnancy and therapy in patients with carcinoma in stage I

Survival	Interval between radiotherapy and pregnancy				
	<1 year	3 years	< 5 years	<10 years	>10 years
5 years	8/10	15/15	2/2	1/1	—
10 years	7/8	11/11	2/2	1/1	—

Table 6

Survival rates after first pregnancy and therapy in patients with carcinoma in stages II and III

Survival	Interval between radiotherapy and pregnancy				
	<1 year	<3 years	<5 years	<10 years	>10 years
5 years	6/10	5/10	1/4	1/1	—
10 years	5/9	3,8	0/1	1/1	—

other delivered two children one and three years after primary therapy and is still alive 23 years later

Fifteen out of seventeen patients who had several pregnancies after treatment for mammary carcinoma were alive 9 to 26 years later Two of these patients died from carcinoma of the breast one 4 years after primary therapy she had had two pregnancies terminated The other patient had been delivered of two children 3 to 5 years after primary therapy and died of metastases 29 years later One patient who had had simple mastectomy combined with postoperative radiotherapy developed a recurrence in the same breast 15 years later this was treated by radical surgery and the patient is now asymptomatic Two patients in whom local excision of the tumour and postoperative radiotherapy were performed subsequently developed recurrences after respectively 5 and 11 years They were treated with radical mastectomy and postoperative radiotherapy One of the two patients is free from symptoms 10 years after primary therapy and the other died from metastases 14 years later The patients in whom metastases of mammary carcinoma were established after pregnancy developed these between 5 months and 11 years after parturition or termination of pregnancy The average interval was 2 years and 9 months

Discussion

Pregnancy following treatment for carcinoma of the breast is remarkably rare The majority of the series published comprise relatively few cases (e g BROWN 1960, MILLER 1962, PETERS 1962, *HEIMAN & BENNETT 1963, DEVITT et coll* 1964, ROBINSON 1965) WHITE (1955) collected 268 cases from the literature As the materials are generally so small and heterogeneous, it has been difficult to decide upon certain important matters that arise in this connection For instance, the stand that should be adopted to pregnancy following treatment for mammary carcinoma is far from clear Some authors (e g LEE 1933) have stated that pregnancy is never desirable after treatment for carcinoma of the breast How ever, *most workers have until recently held the view that pregnancy is contra* indicated for 2 to 5 years after treatment for mammary carcinoma (e g BROWN 1960, ROBINSON 1965, DONEGAN 1967) Pregnancies following soon after treat ment have often been terminated on the strength of this view Another partial reason may be the fact that some mammary carcinomas, though by no means all, grow rapidly in the course of pregnancy as has been demonstrated both *clinically* and in animal experiments (BROMFIS 1939, MCCORMICK & MOON 1965, inter alios) *ADAIR (1953) among others, mentioned the favourable effect* of abortion but this was in a mixed material

The consensus of opinion in the literature is that the first years following upon treatment for mammary carcinoma are the most important for the prognosis Accordingly, patients who become pregnant less than one year after treatment for mammary carcinoma were separated from those who became pregnant within 1 to 3 years, or later Twenty four patients became pregnant earlier than one *year after treatment, and the pregnancy was terminated* in twelve of them

As the series is limited and fairly small, far reaching conclusions are not war ranted However the results seem clearly to suggest that pregnancy after the *treatment of mammary carcinoma affects the prognosis favourably* rather than otherwise provided there are no metastases when the pregnancy begins Six patients had metastases *in the interval between primary therapy for the* tumour and the beginning of pregnancy for which they were treated One of these is alive today, four died 2 to 5 years after primary therapy and one patient died from metastases 25 years after primary therapy The appearance of metastases prior to the start of pregnancy may be a poor prognostic sign If the tumour has been treated and there are no metastases the present results speak in favour of the assumption that whatever the time at which pregnancy begins after the treatment for *carcinoma of the breast it has no unfavourable effect* on the prognosis The author therefore believes that prophylactic ovariectomy should not be recommended or performed regularly in patients with mammary car cinoma

Acknowledgement

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SUMMARY

A series of 53 cases of mammary carcinoma (48 in stages I and II) in which a total of 73 pregnancies occurred have been analyzed. Despite the small series the results seem to indicate that pregnancy has no unfavourable effect on the prognosis for patients with this lesion provided no metastases exist at the time pregnancy begins

ZUSAMMENFASSUNG

Eine Serie von 53 Fallen von Mammacarcinom (48 in Stufen I und II) mit insgesamt 73 Schwangerschaften wurde analysiert. Wenn auch diese Serie klein ist scheinen die Ergebnisse darauf zu deuten dass Schwangerschaft keinen ungunstigen Einfluss auf die Prognose fur Patientinnen mit dieser Lasion hat vorausgesetzt dass bei Beginn der Schwangerschaft keine Metastasen vorliegen

RÉSUMÉ

L auteur a étudie cinquante trois malades atteintes du cancer du sein (dont 45 aux stades I *et II*) qui ont eu au total 73 grossesses. Cette petite serie confirme l opinion que la grossesse n a pas d effet defavorable sur le pronostic du cancer du sein à condition qu il n y ait pas de metastase quand commence la grossesse

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FROM THE DEPARTMENT OF RADIOBIOLOGY AT THE GUSTAF WERNER INSTITUTE AND THE DEPARTMENT OF GYNAECOLOGIC RADIOTHERAPY, UNIVERSITY OF UPPSALA, SWEDEN

WEIGHT CHANGE AND MORTALITY OF RATS AFTER ABDOMINAL PROTON AND ROENTGEN IRRADIATION

A comparative investigation

by

STIG STENSON

Death with evidence of severe intestinal damage such as anorexia diarrhoea and passage of blood will occur 3 to 4 days after the treatment of rats with sufficiently high doses of ionizing radiation to the whole body or the abdomen (BOND et coll 1950) The loss in weight resulting from the damage and the time needed to regain the initial weight seem to be well correlated to the dose (BOND et coll 1950 NIMS & SUTTON 1952 SMITH & TYREE 1954)

As part of a research project aiming at the use of high energy protons for the irradiation of genital carcinoma, the intestinal tracts of rats were irradiated with 185 MeV protons and 220 kV roentgen rays at sublethal and lethal doses The comparison of the radiation effect was based on the weight change and the mortality during a period of four weeks following irradiation

Material and Methods Ninety female rats of the strongly inbred Sprague Dawley strain weighing 220 ± 12 g were used The rats were divided into nine equal groups four groups were irradiated with protons four with roentgen

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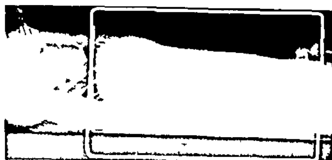


Fig 1 Lateral roentgenogram of a rat showing the position of the rectangular proton field

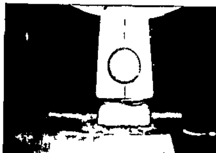


Fig 2 Set up for roentgen irradiation

rays (P rats and X rats) and one served as a non irradiated control The doses were chosen after preliminary experiments so as to give supposedly equivalent effects and to ensure that the range from mild to severe reactions was covered The rats were anaesthetized with about 4 mg/100 g body weight nembutal intra peritoneally, in a solution of 4 mg/ml, and then irradiated with single doses of 720, 850, 920 and 1 120 rad of protons, or 560, 630, 730 and 860 rad of roentgen radiation They were then individually marked in the ears and kept in groups of five in cages with food and water ad libitum The period of observation was 28 days during which the rats were weighed at 1 to 3 day intervals

The *proton irradiation* was performed with a 185 MeV beam from the 230 cm synchro cyclotron, which has been adapted for radiologic experiments as described by LARSSON (1962) The cross section of the beam was a 5 cm × 8 cm rectangle, the absorbed dose and the uniformity of the beam being determined as described by FALKMER et coll (1959) The dose rate was about 350 rad/min and the flux density of the beam was uniform to within ± 15 % The uncertainty in the dose measurement has been estimated to be ± 5 % for protons (LARSSON 1962) The mean linear energy transfer (LET ∞) in the irradiated tissue was about 0 5 keV/μm

The anaesthetized rat lay prostrate on a wooden support during the irradiation The alignment of the animal in the beam was made by means of external landmarks and at each session the position of at least one animal was checked roentgenographically The beam passed through the animal from side to side and all the tissue from the pubis to the diaphragm was irradiated (Fig 1) The animals were observed by television during the procedure No change in position was noted

The *roentgen irradiation* was performed with a Skandia Intensive equipment at 220 kV and 1 mm Al filtration The focus skin distance was 40 cm, the

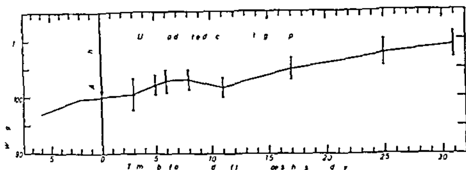


Fig 3 Body weight changes in the control rats The mean body weight at anaesthesia was [illegible]13 ± 5 g

Time before and after irradiation days

Fig 4 Body weight changes in the irradiated rats at doses of 720 rad of protons and 560 rad of roentgen rays Mean body weight at irradiation was for the P rats 2[illegible] ± 11 g and for the X rats 21[illegible] ± 7 g Standard deviations at the individual points

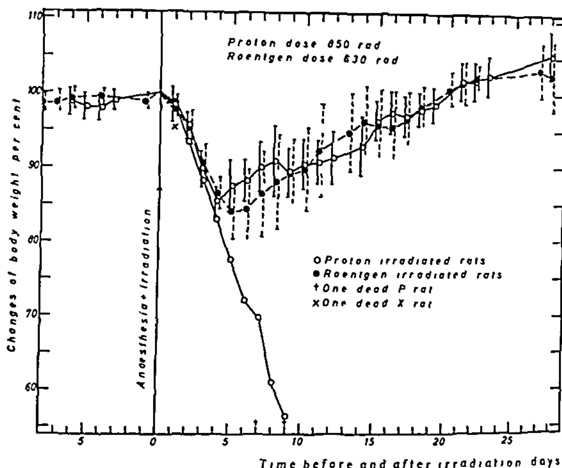
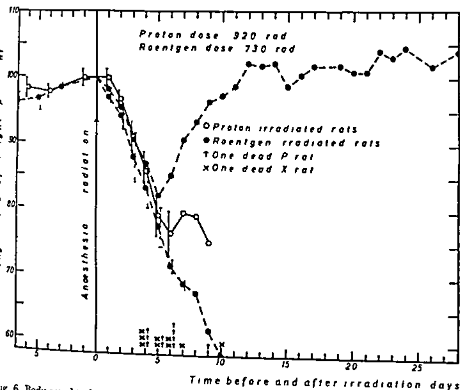


Fig 5 Body weight changes in the irradiated rats at doses of 850 rad of protons and 630 rad of roentgen rays Mean body weight at irradiation was for the P rats 227 ± 9 g and for the X rats 235 ± 7 g Standard deviations at the individual points

average dose rate at the skin being 400 rad/min as determined with an ionization chamber (Philips type 38480 10) The average dose in the peritoneal cavity was 83 % of the surface dose, calculated by a miniature ionization chamber (BENNER et coll 1959) placed at the mid point of a rat-like tissue-equivalent (mix D) phantom The dose values reported are the mid point doses The uncertainty in the absorbed dose was estimated to be ± 10 % for roentgen rays The mean LET ∞ of 220 kV roentgen radiation is 3 keV/μm

The anaesthetized animals lay prostrate on a 2 5 cm thick wooden platform during the irradiation, the abdomen between the pubis and the diaphragm being irradiated from the ventral side through a 5 cm × 8 cm opening in a 6 mm lead shield (Fig 2) The animals were observed through a window during the irradiation No change in position occurred



...ig 6 Body weight changes in the irradiated rats at doses of 920 rad of protons and 730 rad ...f roentgen rays Mean body weight at irradiation was for the P rats 221 ± 15 g and for the ... rats 222 ± 13 g Standard deviations at the individual points

Results

Most of the animals presented evidence of gastro-intestinal radiation sickness ...y the second day following irradiation All the rats that died presented the same ...acroscopic and microscopic appearances dilated blue red intestines filled ...ith blood stained watery liquid loss of the epithelial lining of the mucous mem...rane collapsed villi and a degenerated intestinal wall

Changes in body weight and the times of spontaneous death are given for the ...ontrols in Fig 3 and for the irradiated rats in Figs 4 to 7 The weight curves ...f surviving and non surviving rats from the time of irradiation are given sep...rately in each group Individual deaths are indicated in the diagrams The ...hape of the weight curves of the surviving rats given the lower level doses ...epends on the dose given

At the lowest dose levels of 560 rad of roentgen radiation and 720 rad of pro...ons no significant difference ($p > 0.05$) was recorded between the weights of

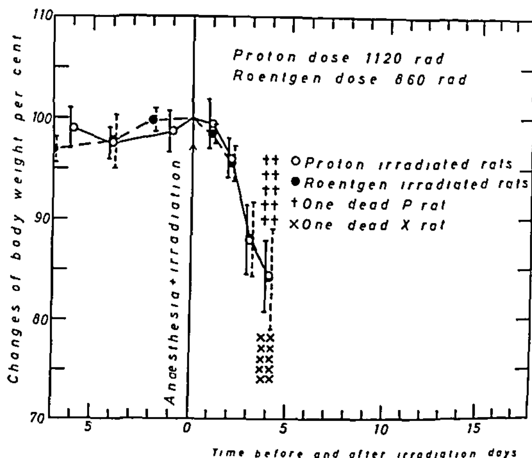


Fig 7 Body weight changes in the irradiated rats at doses of 1 120 rad of protons and 860 rad of roentgen rays Mean body weight at irradiation was for the P rats 22? ± 11 g and for the X rats 227 ± 10 g

the surviving rats at all times of observation selected, with exception for the fifth and seventh days after irradiation (day 5 and day 7), i e during a period in which the rats began to gain weight after the period of anorexia At the second dose levels of 630 rad of roentgens and 850 rad of protons, a statistical difference ($p < 0.05$) was evident only on day 5 (see Table on opposite page)

The statistical significance of the differences between weights not compared in Figs 4 and 5 are obvious from the Table There is a statistical difference between the curves for 560 and 630 rad of roentgen 720 and 850 rad of protons, 560 rad of roentgen and 850 rad of protons from days 4—7 and even between 630 rad of roentgen and 720 rad of protons from day 13

The compared weight curves of the surviving X and P rats thus differ less than the weight curves of consecutive dose groups for the same type of radiation The greatest difference between the survival of P and X rats was observed at

Table

Statistical significance of differences in weight at different times after irradiation of the various groups with respectively roentgen (x) and protons (p) given in rad in the separate columns

Day	560x/720p RBE 0 78	630x/850p RBE 0 74	560x/630x	720p/850p	560x/850p	630x/720p (RBE 0 87)
1	—	—	—	—	—	—
2	—	—	—	—	—	—
3	—	—	—	—	—	—
4	—	—	—		—	—
5	+	+	+	+	—	—
6		—		—		—
7	—	—	+	—	+	—
8	—	—	+	—	+	—
9	—	—	—	+	+	+
10	—	—	+	+	+	—
11	—	—	—	+	+	—
12						
13						+
14	—	—	+	+	+	+
15	—	—	+	+	+	—
16	—	—	+	+	+	+
17	—	—	+	+	+	+
18	—	—	+	+	+	+
19					+	
20						+
21	—	—	+	+	+	+
22	—	—	+	+	+	
23				+	+	
24	—					
25	—					
26						
27						+
28	—	—	+	—	+	+

— No significant difference ($p > 0.05$) + significant difference ($p < 0.05$)

the lowest dose level at which four P rats but no X rats died At the second dose level two P rats but only one X rat died At the third dose level one X rat but no P rat survived At the highest dose level all the X and P rats died on the same day

Discussion

The difficulty in estimating radiation lethality (AUSTIN et coll 1956) indicates that conclusions must be based only on the pattern of weight changes at the two

lowest dose levels where, in addition, the differences in survival are not significant

The observed differences in weight changes or mean survival times were in no case less between two consecutive dose groups for the same type of radiation than the differences between P- and X rats in the pairs of groups compared It may therefore be concluded that the RBE values for the individual pairs of groups should be accurate within a maximum of about 15 %, corresponding to the difference in dose between the statistically different weight curves ($p < 0.05$) The ratios between the compared doses of roentgen and protons are 560/720 = 0 78, 630/850 = 0 74, 730/920 = 0 79 and 860/1 120 = 0 77, respectively

The present results confirm the view held by other investigators that changes in body weight are early and sensitive signs of the gastro intestinal radiation syndrome and may be used as indicators of radiation dosage (cf SMITH & TYREE 1954) This is due to the fact that severe changes in the gastro-intestinal tract occur during the first days following irradiation The first distinct histopathologic changes occur in the small intestine 2 to 3 days after a dose of 600 to 1 200 rad, which causes degeneration of the epithelial lining of the crypts If the dose is high enough, the animal will die from a gastro intestinal radiation syndrome 3 5 to 4 days after irradiation At lower doses, regeneration commences 3 to 4 days after treatment, at which point the period of anorexia ends and the animals begin to gain weight (MONTAGNA & WILSON 1955, QUASTLER 1956)

The two types of radiation used in this investigation initiated qualitatively the same clinical and histologic reactions in the animals, in good agreement with previously reported semi qualitative findings after proton and roentgen irradiation of normal rabbit skin (FALKMER et coll 1959)

Since the ratios between the compared doses of roentgen and protons in the dose range considered are between 0 74 ± 0 15 and 0 79 ± 0 15, the RBE on the intestinal tract of high energy protons (LET ∞ = 0 5 keV/μm) compared to roentgen irradiation of 220 kV (LET ∞ = 3 keV/μm) is 0 77 ± 0 18 The interval of uncertainty may be overestimated

This result is in good agreement with that of other investigators TOBIAS et coll (1952) estimated the RBE of 160 MeV deuterons and 315 MeV protons, as compared with 200 kV roentgen rays, to be approx 1 in mice from the determination of LD 50/30 (the dose causing death of 50 % of the animals within 30 days after irradiation)

The RBE of 170 MeV protons compared with 180 kV roentgen rays for the production of chromosome aberrations in aerated broad beam roots was reported to be 0 70 ± 0 05 by LARSSON & KIHLMAN (1960) BONET MAURY et coll (1960) compared the LD 50/30 of 157 MeV protons with that of 250 kV roentgen rays in mice and recorded an RBE of 0 77 ± 0 1

Hence, in most instances studied the effects of high energy protons have been found to be nearly equivalent to those of other therapeutic radiations of low LET ∞ The present study indicates that this is also true for intestinal damage after local abdominal irradiation a result which should be of particular interest in therapeutic applications of the 185 MeV proton beam for genital carcinomas (FALKMER et coll 1962 FORS et coll 1964) Planning such radiation therapy may thus be based to a great extent on experience gained in conventional radiotherapy

Acknowledgements

The author wishes to thank Prof The Svedberg and Prof John Næslund for their interest in this work particularly the former for providing laboratory resources at his institute Prof Borje Larsson of the Gustaf Werner Institute is thanked for his valuable constructive criticism and Ass Prof B Jung for help with the statistics The investigation was supported by grants from the Swedish Cancer Society and the Swedi h Atomic Research Council

SUMMARY

The intestinal tract of rats was irradiated with high energy protons and their ability to cause weight changes and death was compared with that of equivalent doses of 220 kV roentgen rays No significant differences were found between the two types of radiation Experience from conventional radiotherapy may be used for the application of high energy protons to carcinomas within the peritoneal cavity

ZUSAMMENFASSUNG

Gewichtsverluste und Letalitat bei Bestrahlung des Magendarmtraktes von Ratten mit Hochenergieprotonen bzw 220 kV Rontgen wurden verglichen Kein deutlicher Unterschied zwischen d n beiden Bestrahlungsmethoden wurde festgestellt Demgemass konnen Erfahrungen mit ublicher Rontgenbestrahlung auch bei Protonenbestrahlung von Karzinom der Peritonealhohle zugrunde gelegt werden

RÉSUMÉ

L auteur a irradié l inte tin de rats par des protons de haute énergie il compare l effet des protons sur le poids et sur la mortalité à l effet des doses equivalentes des rayons de roentgen de 220 kV Il n a pas trouvé de différence significative entre ces deux types de radiation On peut ainsi utiliser l expérience de la radiothérapie ordinaire pour l application des protons de haute énergie aux cancers de la cavité peritonéale

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FROM THE DIVISION OF RADIATION SCIENCE, THE NATIONAL PHYSICAL LABORATORY,
TEDDINGTON MIDDLESEX ENGLAND

TRANSISTORISED, BATTERY OPERATED 'DOOR-POST' RADIATION ALARM MONITOR, WITH AUDIBLE AND VISUAL WARNINGS

by

L A W Kemp

A number of gas fired incinerators were installed in individual wards in The London Hospital to deal conveniently and speedily with soiled dressings and other combustible waste Although the main hospital incinerator had been fitted with continuous radiation monitoring facilities to prevent the accidental incineration of radioactive materials (particularly radium sources) the installation of individual ward incinerators constituted a loop-hole with potentially serious consequences in the event of the incineration of a radium source within the main hospital building It was therefore decided to fit each incinerator cubicle door with a radiation monitor the requirements for which could be summarized as follows

1 Battery operation thus avoiding the consequences of possible mains failure

2 Triggering within (say) one second by 0 5 mg radium at (say) 50 cm

3 Basic audible warning to be produced by a method from which for the sake of reliability electro-mechanical contacts were eliminated

4 Instant readiness following switch-on by micro-switches fitted to the incinerator cubicle door

This work was carried out at the London Hospital London England Submitted for publication 18 November 1968

5 Electronic 'locking in' of basic audible warning *in the presence of radiation*, and resetting only when circuit is switched off by closing of cubicle door

6 A secondary (visual) warning (*not necessarily battery operated*), *locking in* and remaining locked in even after monitor switched off by closing of cubicle door

7 Tolerant of background radiation variations, and freedom from the need for background tests

8 No necessity for training of nursing and ward orderly staff in any special operative routine

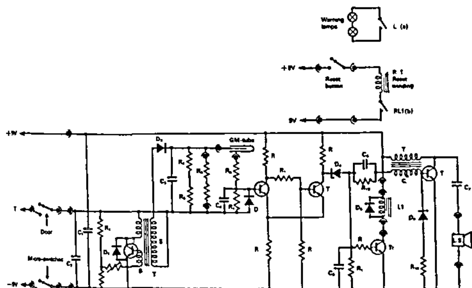
9 Extreme reliability where not inherently *fail safe*, and freedom from false alarms

10 Simple and *inexpensive circuitry to permit minimum maintenance and* full duplication for reliability

Circuit Battery operation and instant readiness requirements indicated the need for a fully transistorised circuit, in which the Geiger Muller H T voltage is provided by a transistor ringing choke converter, enabling the whole circuit (apart from the lamps in the secondary warning device) to be run off one (18 V) battery (the converter in practice being run off the lower half only of the battery)

The circuit is shown in the accompanying diagram

Triggering is catered for by a Schmitt pair, Tr 2 and Tr 3, and electronic locking in is achieved by arranging the reset level of the Schmitt to be unattainable after the circuit has triggered Thus the input signal voltage to the Schmitt comprises the p d developed across part of the G M load This signal runs positive with respect to battery centre tap, and the Schmitt is arranged to trigger at an input level of ~ + 1 5 V The reset voltage is several volts below battery centre tap and although the base current taken by the input transistor of the Schmitt pair (via the high resistance base circuit) is sufficient to bias back the base well below battery centre tap, the base voltage is in fact clamped by a diode and thus prevented from going lower than ~ — 0 5 V The Schmitt once triggered *can therefore be reset only by (at least momentarily)* switching off the supply voltage to the circuit The collector of the second transistor of the Schmitt pair *is coupled* via a *zener* diode to the bases of two *further transistors* one of which (Tr 5) comprises a blocking oscillator, and the other (Tr 4) a conventional common emitter current *amplifier* stage *Both* these transistors are normally off the base circuits being returned to the emitter line When the Schmitt triggers the collector of the second transistor Tr *3* of the Schmitt pair rises towards the + 9 V line, causing the zener diode to conduct and producing forward bias on the succeeding pair of transistors Tr 4 and Tr 5 The blocking oscillator



Circuit diagram of door post radiation alarm monitor

R1 = 6 8KΩ	C1 = 50μF
R2 = 470Ω	C2 = 50μF
R3 = 5KΩ (pre set)	C3 = 0 1μF (1 000V)
R4 = 10MΩ	C4 = 0 47μF
R5 = 10MΩ	C5 = 0 1μF
R6 = 10MΩ	C6 = 50μF
R7 = 10MΩ	C7 = 32μF (100V)
R8 = 2 7MΩ	D4 = 13V Zener diode
R9 = 1 2MΩ	RL1 = Remanence type relay
R10 = 1KΩ (2%)	L S = Miniature (50Ω) loudspeaker
R11 = 1KΩ (2%)	T 1 Core Mullard type LA1
R12 = 2 4KΩ (2%)	Primary (P) 25 turns (40 g)
R13 = 5 6KΩ (2%)	Base (B) 220 turns (40 g)
R14 = 680Ω (2%)	Secondary (S) 2 500 turns (44 g)
R15 = 22KΩ	All wires Lewmex insulated
R16 = 1KΩ	T 2 Ardente type 3034
R17 = 2 7KΩ	
R18 = 220Ω	

transistor is thereby switched on causing a robust loudspeaker condenser coupled to its collector to emit a strong note at a few hundred c p s At the same time the current amplifier stage energises a remanence relay in its collector lead which locks in and via its make contacts switches on the lamps in the visual warning indicator This relay remains locked in magnetically even after the circuit is de-energised and can in fact be reset only by passing a current in the appropriate direction through its reset winding for which provision is made by means of a concealed reset button which connects this winding momentarily across the circuit supply battery

All the transistors are generously rated silicon *n p n* types, and the diodes are also silicon types No finer wire than 44 g is employed in the transformers, and both transformer windings are vacuum impregnated The batteries chosen are cheap and readily available, having screw terminals and soldered internal cell connections The G M tube chosen gives good geometrical coverage of the required doorway area with a 0 5 mg radium needle carried past at walking pace In general, preset components have been avoided in the design, but in one or two places component selection may be necessary (e g the blocking oscillator timing capacitor or resistance)

G M load circuit and Schmitt input circuit The G M tube chosen was a 20th Century G60H, whose operating voltage is 400 V to 500 V The load is a 2 7 megohm and a 1 2 megohm resistor in series, the latter providing the signal voltage, and having a 0 47 μF tank capacitor across it, to give a time constant of about half a second

The potentiometer network connected to the base of Tr 3, the second transistor of the Schmitt pair, provides about 1 5 V at the base of Tr 3 at switch on, and the commoned emitters of Tr 2 and Tr 3 therefore take up a voltage of $\sim + 1\ 0$ V, with the base of Tr 2 at earth potential (Tr 2 therefore being cut off) in the absence of radioactive material (The normal background count rate develops no appreciable voltage across the 1 2 megohm resistor)

When the presence of radioactive material raises the voltage at the base of Tr 2 to about + 1 5 V a regenerative switch over takes place, Tr 2 switching on, and Tr 3 off, very rapidly It can be shown that after triggering the base of Tr 2 would have to be lowered to between —2 V and —3 V for resetting to occur As stated above, the diode D 3 prevents this, and once triggered the Schmitt pair can be reset only by removing the supply voltage momentarily

When Tr 3 switches off as triggering takes place its collector rises from about + 2 V towards + 9 V rail voltage, thereby applying a voltage in excess of the breakdown value to the zener diode D 4, the latter therefore conducting and putting forward bias on the bases of Tr 4 and Tr 5

Blocking oscillator An Ardente D 3034 transformer is used to back couple the collector of Tr 5 to the base circuit (the timing circuit being in the base lead and consisting of a 0 1 μF capacitor in parallel with a 22 k ohm resistor giving an oscillation frequency of about 350 c p s) A 32 μF 100 V capacitor couples the collector to a 50 ohm impedance 3" loudspeaker (situated in the top of the G M tube housing) The employment of an oscillator in conjunction with a loud speaker avoids the use of a bell or buzzer, with their potentially troublesome electro-mechanical contacts

Remanence relay Once energized the remanence relay RL 1 locks in magnetically and remains so even when the operating winding of the relay is subsequently de-energized It can be reset by passing a reverse current through the reset winding for which provision is made by means of a press-button circuit across the 18 volt battery supply This reset button is inconspicuous and unlabelled to avoid irresponsible switching-off of an alarm (A make contact on the relay itself is wired into the reset circuit to ensure a clean and definite resetting action)

DC converter H T supply to the G M tube This is a conventional ringing choke converter the voltage output from which is controlled by the setting of R_3

The H T to the G M counter is set near the top of the plateau to allow for battery fade (the H T falling about 50 V per 1 V supply voltage drop)

To establish the correct value of H T the removeable 20 megohm chain across the reservoir capacitor is withdrawn and a 20 k ohm/V meter on the 1 000 V range substituted for it R_3 is then adjusted to give the correct value of H T and the 20 megohm chain replaced after removing the meter thus compensating for the shunting effect of the latter

Installation as ward incinerator monitors Two complete monitors are installed at each incinerator one on each side of the cubicle door

Four single pole micro-switches are fitted to the door constituting two double pole on-off switches one for each monitor These switches are in the battery centre tap and negative lines respectively to prevent spurious triggering of the Schmitt circuit at switch-on

Each remanence relay has two make contacts available for switching the mains lamps in the visual warning indicator (installed over the cubicle doorway) The latter contains six 15 watt lamps arranged in parallel and illuminating a suitable warning notice The make contacts on the relays are wired in two parallel pairs so as to provide duplicated and independent switching of the lamps A flasher switch in series with the lamps provides an on period of about 2 seconds and an off period of about 1 second and fails safe (i e with lamps on)

Conclusion

Several of these monitors have been in continuous use for nearly four years at The London Hospital and have throughout this period been completely reliable and trouble free

Acknowledgements

The author wishes to express his gratitude to his former colleagues at The London Hospital particularly Messrs B J Banfield and P Bennett for their interest in this project and for helpful discussions

SUMMARY

A simple and inexpensive transistorised door post radiation alarm monitor is described which is battery operated producing both audible and visual warnings The audible warning locks in electronically, and the design eliminates potentially troublesome electro mechanical contacts such as those involved in electric bells and buzzers A remanence relay is employed to lock in the visual warning Several of the monitors have now performed completely trouble free for several years

ZUSAMMENFASSUNG

Eine einfache und billige transistorisierte Tur Pfosten Warnanlage vor Strahlung die Batterie betrieben ist und durch Gerausche und visuell warnt wird beschrieben Die horbare Warnung erfolgt elektronisch und die Ausfuhrung schliesst die potentiellen Storungen elektro magnetischer Kontakte wie sie bei elektrischen Glocken und Summern verwendet werden aus Ein Remanenz Relais ist verwendet um die visuelle Warnung einzuschalten Verschiedene dieser Warnanlagen haben seit einigen Jahren vollstandig störungsfrei gearbeitet

RESUMÉ

L auteur décrit un dispositif d alarm aux radiations transistorisé simple et peu couteux fonctionnant sur pile qui produit des signaux auditifs et visuels L avertisseur sonore est enclanché électroniquement et sa construction élimine les contacts électro mécaniques qui pourraient etre genants tels que ceux des sonnettes électriques et des vibreurs Un relai a remanence est employé pour enclancher l avertisseur visuel Plusieurs de ces avertisseurs ont maintenant fonctionné pendant plusieurs années sans aucune difficulte

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RETICULUM CELL SARCOMA TREATED BY RADIOTHERAPY

Significance of clinical features upon the prognosis

by

HANNE SAND HANSEN

The prognosis in reticulum cell sarcoma depends as in all malignant disease upon the condition of the patient when first seen on the ext of the lesion and its histologic type and on the effectiveness of the treatmen All these clinical f atures have been considered in a review of a large material examined over a period of more than 25 years

Material A total of 265 patients with histologically verified reticulum cell sarcoma 225 of these without any previous treatment have been treated and followed at the Radium Centre of Copenhagen during the period 1940—1966 Of these patients 40 % had been referred from the capital Copenhagen 24 % came from its suburbs and only 12 % were drawn from provincial towns and 24 % from the rural districts The Radium Centre serves a population of nearly two million people in all

From the Radium Centre Copenhagen Denmark

Part of this work was presented at the ?th Congress of the Scandinavian Radiologic Society Copenhagen ?9 May—1 June 1968 Submitted for publication 23 December 1968

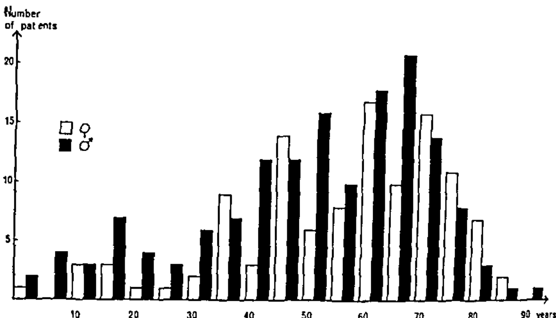


Fig 1 Age and sex distribution of 265 patients with reticulum cell sarcoma

Only patients with lymphoglandular involvement are included in this survey During the same period, 1940—1966, treatment was being given to 108 patients with lymphosarcoma, 465 patients with Hodgkin s disease and 22 patients with the diagnosis of giant follicular lymphoma have been treated Thus, the patients with reticulum cell sarcoma total 31 % of the malignant lymphomas treated In other publications the reticulum cell sarcomas amount to from 19 6 % to 26 4 % of the malignant lymphomas treated (JACKSON & PARKER et coll 1947, GALL 1941)

Reticulum cell sarcoma is more frequent in males and the present material indicates a sex distribution of 151 males 114 females, i e 57 % males The percentage of men has been reported as varying from 54 % to 66 % (STEJSKALOVA 1968 SYMMERS 1966)

All ages are represented, the youngest patient being one year and the oldest 94 years old Like all sarcomas, it more often occurs in old age As will be seen from Fig 1, the age distribution of men and women in our material was more or less equal, with a predominance of males in the first decades This was also reported by ROSENBERG et coll 1960) The average age in our material was 54 2 years (51 8 years for males and 57 5 years for females)

Symptoms and Signs Painless enlargement of cervical lymph nodes is the commonest presenting feature but it was noticeable that delay in reporting symptoms

Table I A

Extent of the disease in lymphoma cases

Region initially involved	Right side		Left side		Both sides*		Total	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Neck	106	40.0	124	46.8	55	20.8	175	66.0
Supraclavicular	58	21.8	71	26.8	30	11.3	99	37.4
Infraclavicular	8	3.0	15	5.7	2	0.8	21	8.0
Axilla	79	29.8	85	32.0	52	19.6	112	42.3
Mediastinum							24	9.1
Pulmonary hila	[illegible]	[illegible]	32	12.1	30	11.3	34	12.8
Inguinal	65	24.5	67	25.2	51	19.[illegible]	81	30.6
Crural	22	8.3	25	9.4	10	3.8	37	14.0
Abdominal							38	14.3

* Included in the first two columns

Table I B

Organs involved in addition to the lymph nodes

Region	Clinical series (265 patients)				Autopsy series (87 patients)	
	Initial involvement		Later involvement		Number	Per cent
	Number	Per cent	Number	Per cent		
Lung	26	9.8	11	4.1	20	23.0
Liver	24	9.1	8	3.0	22	25.2
Spleen	14	5.3	[illegible]	2.3	22	25.2
Bones	23	8.7	7	2.6	13	15.0
Soft tissue	25	9.4	10	3.8	4	4.6
Skin	17	6.4	5	1.9	4	4.6
Parotid	17	6.4	2	0.8	0	
Pharynx	12	4.5	8	3.0	2	2.3
Tongue	8	3.0	2	0.8	2	2.3
Nose	3	1.1	1	0.4	0	
Gastro-intestinal	6	2.3	2	0.8	14	16.0
Uro-genital	6	2.3	2	0.8	32	36.8
Other	6	2.3	5	1.9		

varied considerably amongst the patients so that although two-fifths were seen within 2 months and four fifths within 6 months a smaller number (2 %) delayed consultation for up to 4 years

Table 2

Distribution of patients in the four stages made out for each patient from the information of the clinical records at the admission

Groups		Stages			
		I	II	III	IV
1 A		52	13	23	89
1 B		1	1	11	33
2 A		13	23		
2 B		0	6		
	Total	66	43	34	122

Glandular enlargement was the reason for seeking advice in 77 % of the patients, and 14 % complained of pain In half the number of the latter, the pain was in the abdomen, often due to glandular enlargement or hepatosplenomegaly, in a quarter it was due to pressure on peripheral nerves and in a little less than a quarter it was associated with bone involvement

General signs or symptoms were present in 20 % of the patients, such as fever over 38° C for more than one week, anorexia with loss of more than 10 % of body weight, or sweating, particularly at night KAPLAN *et coll* (1964) also included anaemia as a general sign, which has not been done here

Location of the disease at the time of admission The lymphomas most often appear in the upper part of the neck (excluding the supraclavicular regions) (see Table 1-A) On the first admission, 66 % of the patients had lymphoma in the upper neck, in 29 % involving the right side only, and in 40 % the left side, while only 31 % of the patients had both sides of the upper cervical region involved The supraclavicular regions were affected in 37 % of the patients HARE et coll (1948) reported enlargement of lymph nodes of the neck as the first sign in approximately 61 % of patients

Next to the neck, the axilla is the most common primary location, while the inguinal region is rarely involved initially This contrasts with the series of HOLLARD (1960) and BOUSSER (1966), who found that reticulum cell sarcoma presented more often in the inguen than in the axilla

Involvement of organs in addition to lymph nodes occurred in 46 % of the patients (see Table 1 B) Hepatomegaly occurred more often than splenomegaly, and at the time of admission changes were more frequent in the lungs than in the bones These proportions held true in the autopsy series as well (Table 1 B)

Staging An international classification of reticulum cell sarcoma has not yet been published by UICC but at the international symposium in Paris held in February 1965 with Professor M Tubiana as president it was decided to follow the stage classification for lymphogranulomatosis maligna Hodgkin This was later (in September 1965) confirmed by the Westchester Symposium at Rye near New York according to which the recommendation got the name of the Paris-Rye system (LAUGIER 1966) The present material has therefore been staged as follows

	Stage
Disease limited to one anatomic region	I—1
Disease limited to two contiguous regions	I—2
Disease in two non-contiguous regions on the same side of the diaphragm	II—1
Disease in more than two anatomic regions on the same side of the diaphragm	II—2
Disease on both sides of diaphragm including the spleen and Waldeyer's ring	III
Involvement of bone bone marrow lung parenchyma pleura liver and any tissue or organ in addition to lymph nodes spleen and Waldeyer's ring	IV

All stages are subclassified as A or B to indicate the absence or presence respectively of the general symptoms or signs defined above (ROSENBERG 1966)

The distribution of the patients between the four stages made out retrospectively for each patient from the information of the clinical records at the time of admission is given in Table 2 The great number of patients belonging to stage IV and the total group B indicates that a rather selected group of patients was accepted for treatment in this period No patients have been excluded not even those receiving only a few days palliative treatment

The age and sex distribution in the four stages are recorded in Table 3

Treatment The treatment has mainly been roentgen irradiation to the involved area, carried out in a single series Only 44 patients have been treated with chemotherapeutic agents as well Even in advanced or incurable conditions semiradical irradiation was given to all the involved areas and proved worthwhile since subjective improvement was often achieved No other treatment produced better results

Referred without any former treatment were 225 patients 40 patients had been treated in other departments prior to admission but only 14 of these required no further therapy The treatment factors were 180 kV roentgen irradiation (HVL 1 2 mm Cu and FSD 40 cm) or 250 kV (HVL 2 4 mm Cu and FSD 50 cm) Not until 1965 was the Radium Centre able to treat all reticulum cell sarcomas with ^{60}Co irradiation

Table 3

Age and sex distribution of the patients with lesion in the four different stages

Age years	Stage I		Stage II		Stage III		Stage IV		Total		
	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	all
1—9	1			1		1		4	1	6	7
10—19	1	1		2		2	5	5	6	10	16
20—29	2	3		1		1		1	2	6	8
30—39	6	2	2	4		4	3	3	11	13	24
40—49	1	5	1	4	2	8	13	7	17	24	41
50—59	8	2		8	1	2	5	14	14	26	40
60—69	9	8	5	5	3	5	10	21	27	39	66
70—79	9	6	5	4	1	3	12	9	27	22	49
80—89	2			1	1		6	3	9	4	13
90								1		1	1
Total	39	27	13	30	8	26	54	68	114	151	265
	66		43		34		122		265		

Table 4

Initial hematologic values in total number of patients/percentages of stages

	Stage I	Stage II	Stage III	Stage IV	Total number	% of total
Hemoglobin						
>90	43/65.1	20/46.5	11/32.3	52/42.6	126	47.5
70—89	21/31.9	19/44.2	20/58.9	61/50.0	121	45.7
<69	1/1.5	1/2.3	3/8.8	8/6.6	13	4.9
Unknown	1/1.5	3/7.0	0	1/0.8	5	1.9
Sedimentation rate in mm						
10	22/33.3	11/25.6	10/29.4	21/17.2	64	24.2
10—39	32/48.5	15/34.8	13/38.2	49/40.2	109	41.1
>40	11/16.7	14/32.6	11/32.4	50/41.0	86	32.4
Unknown	1/1.5	3/7.0	0	2/1.6	6	2.3
White blood cell count in mm						
4 000	6/9.1	7/16.2	6/17.7	23/18.9	42	15.8
4—10 000	55/83.3	30/69.8	23/67.6	79/64.7	187	70.5
>10 000	2/3.1	3/7	4/11.8	12/9.8	21	8.0
Unknown	3/4.5	3/7	1/2.9	8/6.6	15	5.7

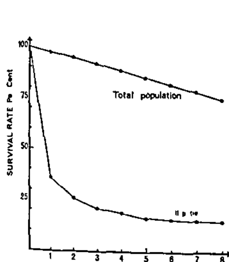


Fig 2 Survival rates for all patients with reticulum cell sarcoma compared with the expected survival rates for the total population of the same age and sex distribution

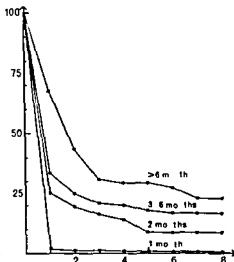


Fig 3 Survival rates according to the duration of symptoms before the patients sought advice

Results

The overall mortality indicates a 5 year survival rate of 16 3 % (Fig 2) The death rate was highest during the first year of observation and later decreased more slowly after 3 years approaching the natural mortality from all causes for the general population of the same age and sex distribution based on a 5 year statistical information from the middle of the period 1940—1966 Not all the patients have been observed for 5 years 20 patients treated in the period 1963—1966 have not so far completed the 5 year survival so the curve has been based on the time of observation for the surviving patients

Long surviving patients Twenty two patients 7 males and 15 females have so far lived for more than 10 years and eighteen patients are still alive Two patients eventually died from their disease and two from other causes

Fourteen patients belong to stage I and of these eleven had lymphoma in the upper part of the neck two patients had lymphoma in the inguinal region and one in the axilla FULLER et coll (1962) reported a 44 8 % 5 year survival for lymphomas in the head and neck against 47 3 % for the whole of stage I The primary location apparently produced no difference in the survival

Table 3

Age and sex distribution of the patients with lesion in the four different stages

Age years	Stage I		Stage II		Stage III		Stage IV		Total		
	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	
1— 9	1			1		1		4	1	6	
10—19	1	1		2		2	5	[illegible]	6	10	
20—29	2	3		1		1		1	2	6	
30—39	6	2	2	4		4	3	3	11	13	
40—49	1	5	1	4	2	8	13	7	17	24	
50—59	8	2		8	1	2	5	14	14	26	
60—69	9	8	[illegible]	5	3	5	10	21	27	39	
70—79	9	6	[illegible]	1	1	3	12	9	27	22	
80—89	2			1	1		6	3	9	4	
90								1		1	
Total	39	27	13	30	8	26	54	68	114	151	2[illegible]
	66		43		34		122		265		

Table 4

Initial hematologic values in total number of patients/percentages of stages

	Stage I	Stage II	Stage III	Stage IV	Total number	of total
Hemoglobin						
>90	43 /65 1	20/ 46 5	11/ 32 3	52/ 42 6	126	47 5
70—89	21/ 31 9	19/ 44 2	20/ 58 9	61/ 50 0	121	45 7
<69	1/ 1 5	1/ 2 3	3/ 8 8	8/ 6 6	13	4 9
Unknown	1/ 1 5	3/ 7 0	0	1/ 0 8	[illegible]	1 9
Sedimentation rate in mm						
10	22/ 33 3	11/ 25 6	10/ 29 4	21/ 17 2	64	24 [illegible]
10 –39	32/ 48 5	15/ 34 8	13/ 38 2	49/ 40 2	109	41 1
>40	11/ 16 7	14/ 32 6	11/ 32 4	50/ 41 0	86	32 4
Unknown	1/ 1 5	3/ 7 0	0	2/ 1 6	6	2 3
White blood cell count in mm						
4 000	6/ 9 1	7/ 16 2	6/ 17 7	23/ 18 9	42	15 8
4—10 000	55/ 83 3	30/ 69 8	23/ 67 6	79/ 64 7	187	70 5
>10 000	2/ 3 1	3/ 7	4/ 11 8	12/ 9 8	21	8 0
Unknown	3/ 4 5	3/ 7	1/ 2 9	8/ 6 6	15	5 7

Of the patients with stage II lesions only three survived fore more than 10 years, one with subdiaphragmatic and two with supradiaphragmatic lymphomas Only two of the total number of patients with stage II lymphoma had the lesion below the diaphragm

Only five patients in stages III and IV survived for 10 years one patient in stage III and four patients in stage IV

Factors influencing the prognosis

Duration of symptoms A short history is often associated with a poor survival (Fig 3) This may be explained as follows if symptoms after only a month are so alarming that the patient consults a doctor the disease is progressing so rapidly that it will probably be hard to arrest On the other hand CACHIN et coll (1966) reported a 71 % 1 year survival for patients having symptoms for a month and a 33 % 1 year survival rate for patients with symptoms more than 6 months

Sex and Age An examination of Fig 4 (upper left diagram) which presents the survival curves indicates that the prognosis for females is a little better than for males especially considering the better survival for males in the total population of the same age and sex distribution The better survival for females has been reported by many others including ROSENBERG et coll (1961) EASSON & RUSSELL (1963) and JELLIFE (1966)

The younger patients under 40 years of age do somewhat better as is apparent from Fig 4 (upper right diagram) In this group the 20 to 39 years old patients had the best prognosis in spite of the slight predominance of males in this age group The same results have been reported by PETERS (1963)

Or the whole patients over 60 years of age have the smallest chance of survival (even considering the high natural mortality in this age group) The poorest prognosis occurs in women over 60 years so in this group the women s relatively better prognosis does not hold good This has also been stated by EASSON (1966)

Extent of the disease The influence of the extent of the disease on the survival rate is apparent from Fig 5 For stage I the survival rate after 5 years is 45 7 % for stage II it is 19 5 % and for stage III 0 6 % while stage IV has a 5 year survival rate of 3 8 % The dominance of males in stage III contributes to the poor prognosis as will be clear from a study of the sex distribution in the different stages (cf Table 3)

Patients in stage IV with disease in the skin stomach intestine and certain organs of the head and neck such as the tongue the pharynx and the parotid glands have presented a far better prognosis than the remaining stage IV pa

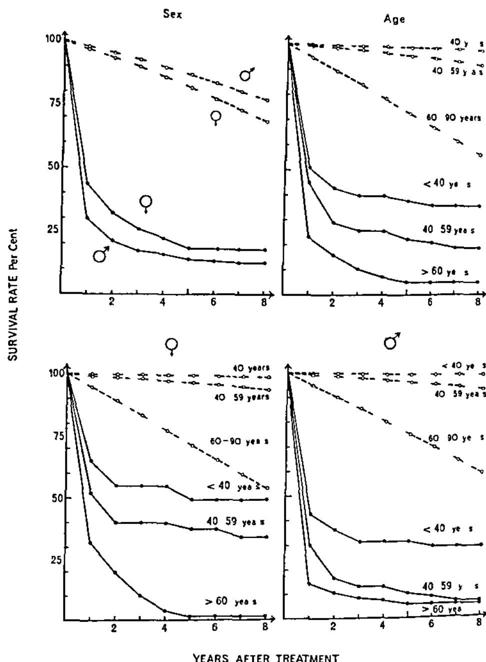


Fig 4 Survival rates for patients with reticulum cell sarcoma according to sex and age (upper diagrams) and sex + age (lower diagrams) as indicated by solid lines The total mortality for the population of the same age and sex distribution is presented for comparison (dotted curves)

tients The 5 year survival rate for these locations has been between 10 % and 22 % Patients, 180 in all with the condition primarily located to Waldeyer s ring have been excluded from this study

The survival curves for stages I—A, II—A and III—A and for patients with initial general symptoms (dotted curves) in stages I—B plus II—B plus III—B are given in Fig 5b The curve for the nineteen patients with general symptoms at the time of admission is very steep None of the patients lived longer than 15 months

Laboratory findings Abnormal hematologic findings occurred in a number of patients before the treatment started The percentages of pathologic values were roughly the same in all stages of the disease as seen from Table 4 Normal values slightly predominated in stage I and abnormal values in stages III and IV

About half the number of patients had normal hemoglobin levels but only a quarter of all the patients had normal sedimentation rates A third of the pa tients had a sedimentation rate of more than 40 mm and eighteen out of 265 patients i e 7 % had a sedimentation rate of more than 100 mm

There were normal WBC levels in 70 % of the patients only 16 % of the pa tients had below 4 000 leucocytes per mm³ and 8 % of the patients WBC values between 10 000 and 37 000 per mm³ Marrow aspiration was made in 65 % of all the patients Of these 5 2 % had tumour cells and 3 5 % leukemic infiltra tion and only half the number of these patients had an elevated WBC in the per ripheral blood Proliferation of reticulum cells was present in 21 5 % and mye lopoietic hyperplasia in an additional 17 % of the patients Thus marrow hyper plasia seems to be as common in this group of reticulum cell sarcoma as in Hodg kin s disease (GORMSEN 1942) Diffuse marrow hypoplasia occurred in 7 % of patients in the present material whereas 45 % had normal marrow

The importance of hematologic abnormalities in the prognosis is evident from Fig 6 a. Even a slightly reduced level of 70 % to 89 % corresponding to 10 4 to 13 2 grampercent must be considered as a sign of a more advanced stage than the objective examination has proved Not only slight anaemia but also a small elevation in the sedimentation results lead to a decrease in the survival rate (Fig 6b) The survival curves related to the WBC are given in Fig 6c A poorer survival rate occurs in patients with abnormal white blood cell counts, cor responding to the results of BERNARD (1966) and BOUSSER (1966) who both reported a poorer survival rate in patients with leucopenia compared to patients with a normal WBC

Histologic type The histologic appearances of reticulum cell sarcoma are com plex All patients underwent biopsy and the pathologic diagnosis with a varying degree of certainty was reticulum cell sarcoma The evaluation was uniform as

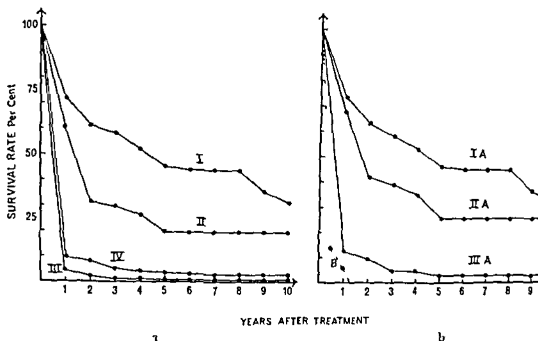


Fig 5 Survival rates in stages I II III and IV (left diagram) and in stages I—A II—A III—A and B = I—B + II—B + III—B (right diagram)

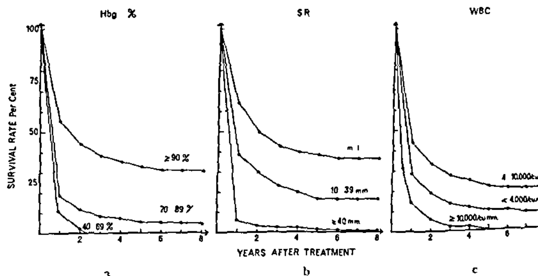


Fig 6 Survival rates according to initial blood values hemoglobin per cent (a) sedimentation rate (b) and white blood cell count (c)

The twenty two patients classified as belonging to the giant follicular lymphoma group in this material had a 5 year survival rate of 56 4 % (see Fig 7)

Progression from follicular to diffuse lymphoma may take place after a variable period of time Two or more biopsies were performed during the period of disease in only five patients of this group In three of these patients the first biopsy revealed follicular lymphoma and the second infiltrating reticulum cell sarcoma In the two other patients the opposite development apparently occurred as the first biopsy disclosed reticulum cell sarcoma while the second biopsy indicated giant follicular lymphoma A similar case has been mentioned by DORFMAN (1964)

The difficulties in making the correct diagnosis appear from the mistakes revealed by autopsy Twenty eight patients have been omitted from this survey because autopsy produced a different diagnosis (four diagnoses were corrected during the lifetime of the patient) The list of the patients omitted is given below

	Number of patients
Melanoma malignum	2
Carcinoma bronchogenes pulmones	2
Carcinoma ventriculi anaplasticum	2
Sympatoblastoma	2
Myelomatosis	1
Thymoma	1
Carcinoma ovarii	1
Carcinoma prostata	1
Carcinoma testis	1
Seminoma testis	1
Carcinoma thyreoidea anaplasticum	1
Retinoblastoma	1
Lymphadenitis tuberculosa	1
Hemangioendothelioma malignum	1
Lymphogranulomatosis Hodgkin	10

These erroneous diagnoses appeared in a total of 115 autopsy records in most instances as metastases from a primary occult tumour with histologic appearances of a high degree of anaplasia The difficulties were pointed out by LUMB (1954) and by STEJSKAL et coll (1966) who stated that the reticulum cell sarcoma diagnoses made during life were wrong in a quarter of patients over 60 years of age and in half the number of those over 70 years of age

Malignant diseases of different types were diagnosed during life in twelve

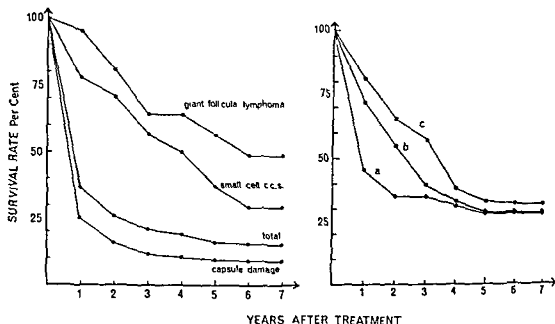


Fig 7 (left) Survival rates according to the histologic type of lesion giant follicular lymphoma small cell reticulum cell sarcoma and reticulum cell sarcoma with spread outside the capsule being compared with the survival rate of all patients with reticulum cell sarcoma

Fig 8 (right) Survival rate of patients with reticulum cell sarcoma according to varying degrees of radiosensitivity a) High degree of radiosensitivity The tumour disappeared before 2 000 R was given b) Tumour was radiosensitive and disappeared during the first treatment series c) Slow disappearance of tumour over 1 to 6 weeks after the treatment ended

more than 85 % of the material was seen by either of the two senior pathologists during the 26 year period

A division of the tumours according to the degree of anaplasia produced no clear influence on the survival rate

Extension outside the capsule leads to a poorer prognosis (Fig 7) On the other hand, lymphomas consisting of small uniform cells between 5 and 15 μ present a better prognosis This is perhaps not surprising as these growths are, like lymphosarcomas more radiosensitive and associated with a better survival rate (COOK et coll 1960 PETERS 1963)

A lymphoma with a follicular arrangement is identical with the giant cellular lymphoma commonly known as Brill Symmers disease, after BRILL & ROSENTHAL (1925) who defined this category of lymphomas as an entity and SYMMERS who in 1927 published 3 cases Not until later was it clearly stated that the disease was of a malignant character (ROSENTHAL et coll 1933) After RAPPAPORT (1956) it is more often classified as malignant lymphoma of the follicular type

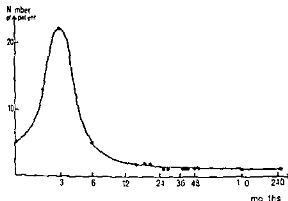


Fig 9 Number of patients with recurrences at different intervals after the first treatment

limited changes could be expected to survive long enough to allow evaluation of the effect of the irradiation About a third of these patients had generalized disease and died within the first year of the primary treatment The radiation effect was therefore studied in those stage I and stage II patients who survived for a year or more The time dose relationship for 49 patients in whom the tumour dose could be calculated is given in Fig 10 All but one have been followed for five years or more For comparison the tumour lethal dose for skin cancer as given by STRANDQVIST is indicated by the solid line In spite of the fact that this approximate fractionation curve only holds good for equally fractioned low voltage treatment to small superficial fields and that only a small number of patients is involved it appears that the reticulum cell sarcoma exhibits greater radiosensitivity than skin cancer

The average dose for these patients was 2 800 R over 33 days, or a dose rate of approximately 600 R per week This according to FULLER et coll (1962), is too low a rate as she experienced local recurrences more frequently when the tumour dose rate was less than 750 rad per week even if the relative biologic efficiency for kilovoltage and high voltage irradiation was taken into account Likewise PATERSON (1963) stated that experience had indicated that after 2 000 rad or less over three weeks the majority of growths will recur not only at other sites but in the treated zone itself

The mean dose for tumour control is dotted in Fig 10 The slope of the curve on the log log graph is 0 45 it represents the calculated recovery factor for stage I and stage II reticulum cell sarcoma Slopes higher than 0 20 represent significant recovery according to FRIEDMAN (1967)

The eight recurrences developed from 3 to 15 months after the primary treatment The recurrences were evenly spread according to the overall treatment times

Table 5

Number of recurrences following the initial treatment

	Total number of patients in resp stages	Local recurrence	Recurrence at a new site	Both local and distant recurrence
Stage I	66	6	18	3
Stage II	43	0	14	2
Stage III	34	6	5	4
Stage IV	122	12	26	6
Total	*265*	*24*	*63*	*15*

patients, or in 4 5 % of the series Co existent cancer was noted post mortem in two patients

Radiosensitivity It is generally accepted that the reticulum cell sarcomas are extremely radiosensitive, a postulate which is only partly true Only two-thirds in all of the lymphomas disappeared after adequate roentgen treatment In this radiosensitive group, 11 % vanished like dew in the sun, while 44 % disappeared *in the course of treatment* and 45 % exhibited delayed resolution *It is remark*able that of all the tumours that regressed, nearly half disappeared within one to six weeks after the completion of treatment

It was noted that those tumours that were sensitive to radiation and resolved quickly during treatment were not necessarily those which subsequently proved to be curable by irradiation, and that a high degree of radiosensitivity does not improve the prognosis (Fig 8) Similar observations have been made by other authors (PETERS 1963)

Recurrence Recurrence took place in all four stages, as may be seen from Table 5 A recurrence was detected and treated *in 102 patients* of which 24 patients had recurrence at the primary treatment region and an additional 15 patients developed local recurrence together with recurrence at a new site

The recurrences came quickly, so that 40 % of them developed within 3 months 70 % within 6 months and 85 % within one year after the initial treatment Only three patients had recurrences after 4 years, but in one instance an interval of 22 years was recorded As indicated in Fig 9, there was a logarithmically normal distribution of the time lag for the development of recurrences, with a median value of 3 months

Further analysis was carried out for the 109 patients in stages I and II, in order to evaluate the radiocurability of reticulum cell sarcomas Only patients with

for so long Of all those treated for recurrences 32 % have lived for more than a year after the second treatment series Generalization of the disease occurs not only in stages III and IV but also in the early stages since one third of the patients in stages I and II, in whom the disease became general often rather suddenly died within weeks or months

Discussion

The results of treatment in this series are difficult to compare with other published reports The overall results depend not only upon the effectiveness of the therapeutic technique but also to a high degree on the initial condition of the patients at the time of the first treatment course The results will only be comparable with those in groups of patients presenting the same relative ratio of stages age and sex Furthermore the blood values, the histologic type and the length of the history must be comparable for a valid assessment

More patients in this material had advanced disease than in most other published series and the average age is higher This may explain why the overall 5 year survival rate of 16 3 % is somewhat lower than the 22 6 % reported by ROSENBERG et coll (1961) while it compares favourable with the figure of 6 % given by JACKSON (1947)

The inclusion of all malignant lymphomas usually raises the overall 5 year survival rate e g to 17 1 % as given by STOUT (1947) or 38 4 % by FULLER (1962) The treatment used was in FULLER s series partly supervoltage and partly orthovoltage irradiation Likewise LAUGIER (1966) reported a 30 6 % 5 year survival rate for reticulum cell sarcoma and lymphosarcoma after treatment with telecobalt or a 6 to 8 MeV linear accelerator ROSENBERG (1961) reported a 28 4 % 5 year survival in a predominantly kilovoltage roentgen treated group of lymphomas In the whole series of malignant lymphoma the survival rate for reticulum cell sarcoma is therefore the poorest

The treatment results ideally should be compared stage to stage but unfortunately earlier publications often use other staging systems PETERS staging for Hodgkin s disease in 1950 was different from the one used here as was her staging for lymphoma in 1963

Some publications distinguish only between localized and generalized disease the latter form being equivalent to PETERS stage III which in this material is comparable with stage III plus stage IV Likewise, EASSON (1966) reported a 50 6 % 5 year survival for localized lymphoreticular sarcoma and LAUGIER et coll. (1966) a 48 1 % 5 year survival for localized disease against 12 6 % for generalized disease in two equally large groups of lymphoreticular sarcomas Only the stage I—1 plus I—2 plus II—1 reticulum cell sarcoma can be called

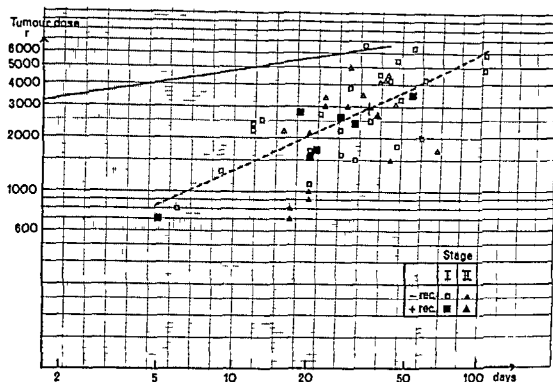


Fig 10 Time dose relationship for patients with lesions in stages I and II and with stated tumour dose who survived a year or more Open symbols indicate local control and solid symbols local recurrence The mean curve for tumour control is dotted A curve constructed from the data of STRANDQVIST for mean accumulated lethal tumour dose for cancer of the skin is included for reference

as well as to the tumour dose concerned Five of the patients were women, 80 % of whom were over 60 years old, and three were males two of whom were over 60 Only three lived for more than 2 years after the first treatment series and only one is still alive 23 years later Of the 33 patients without a stated tumour dose (not shown in Fig 10) only three developed recurrences

As is evident from Fig 10, no ideal treatment time can be determined and this is also true for the total material, since a third of the local recurrences developed in patients treated for less than 3 weeks, another third in the patients in whom the treatment lasted from 20 to 40 days, and in the remainder in patients in whom the treatment course lasted from 6 to 14 weeks

MOLANDER & PACK (1965) stated that response to the first course of treatment is better Of the patients in the present series who were treated for local recurrences, 40 % have lived for more than a year, whereas only 29 % of the patients with recurrences treated in regions other than the primary site have lived

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localized in the present material, and these 80 patients had a 5 year survival rate of 51.6 %.

Treatment policy. No prophylactic irradiation of the clinically uninvolved contiguous lymph node regions has been carried out and from the literature it would seem of doubtful value in reticulum cell sarcoma. HAN & STUTZMAN (1967) reported a 48 % distant spread but only 26 % adjacent spread. Likewise, PETERS (1963) demonstrated no increase in survival following prophylactic irradiation of both sides of the neck if one side was affected, as well as prophylactic therapy of mediastinum if the supraclavicular fossa was involved.

The dose given has been individualized, since it has been varied according to the clinical effect. Since 1965, cobalt irradiation has been given to all patients with reticulum cell sarcoma, with doses up to the level recommended by FULLER (1967) and LERFBOULLET (1966), i.e. not less than 5 000 R over 5 weeks.

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The author wishes to thank H. Johansen (Radium Centre, Copenhagen) for help and advice, J. Rygard (Radium Centre, Copenhagen) for his encouragement, access to the material, help and instructive discussion, and A. I. Broad (Royal Marsden Hospital, London) for assistance with the English version.

SUMMARY

A material of 265 patients with lymphomas histologically verified as reticulum cell sarcoma treated during the period 1940—1966 is reviewed and staged according to the Paris—Rye system. The treatment is described. The significance of the histologic type and the difficulty of making a correct diagnosis are discussed.

ZUSAMMENFASSUNG

Ein Material von 265 Patienten mit histologisch bestätigtem Retikulosarkom der Lymphdrüsen, die zwischen den Jahren 1940—1966 behandelt wurden, wird kritisch besprochen und nach dem Paris—Rye System in Stufen eingeteilt. Die Behandlungsart wird beschrieben. Der Wert der histologischen Klassifizierung und die Schwierigkeiten eine genaue Diagnose zu stellen sowie die Faktoren, die die Prognose beeinflussen, werden diskutiert.

RÉSUMÉ

L'auteur passe en revue une série de 265 malades atteints de lymphome dont l'examen histologique a montré qu'il s'agissait de sarcomes à cellules réticulaires et qui ont été traité entre 1940 et 1966. Il décrit le traitement. Il examine l'importance du type histologique et la difficulté de faire un diagnostic correct.

FROM THE RADIOTHERAPY CLINIC (DIRECTOR PROF L R HOLSTI) UNIVERSITY CENTRAL HOSPITAL, HELSINKI FINLAND

CLINICAL AND RADIOTHERAPEUTIC ASPECTS OF RETICULUM CELL SARCOMA

by

URPO TIKKA and KAI MALMIO

The results of radiotherapy of malignant lymphomas appear to have gradually improved during recent years which may be partly attributable to the increased use of megavoltage therapy The possibilities of improving the therapeutic results by means of prophylactic irradiation have also been discussed (EASSON 1967 JACOBS 1968) This means that the lymph gland regions involved as well as surrounding areas are included in the treatment programme The significance of prophylactic irradiation in the treatment of Hodgkin s disease is generally recognized but there is little common agreement as regards such treatment in cases of lymphosarcoma or reticulum cell sarcoma

Attention in the present studies was mainly directed towards establishment of the possible sites of secondaries and the chronologic sequence of the primary neoplasms treated locally An attempt was also made to note the sites of predilection if any, with a view to possible prophylactic irradiation

Material and Methods The material consists of 154 reticulum cell sarcoma cases registered during the period 1951—1962 The diagnosis was based on microscopic examination in every instance Histologic verification was not always

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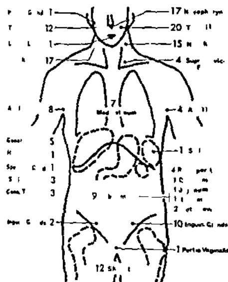


Fig 2 Distribution of the series by the primary site of the tumour

The distribution within this classification in the present material was stage I for 94 cases stage II for 44 cases and stage III for 16 cases

Therapy Most of the patients were treated with orthovoltage roentgen rays but twenty-one patients received teleradium treatment and seven telecobalt radiation

In the treatment of nodes in the neck and in axilla or groin the factors were 180 to 190 kV 0 5 mm Cu filter and 40 cm focus-skin distance and in the treatment of mediastinal abdominal and bone tumours 230 to 250 kV 1 mm Cu filter and 60 cm FSD The most common field sizes were 6 cm×8 cm and 8 cm×10 cm The daily field dose on the skin was 250 to 350 rad most often two converging fields were used The tumour dose in the entire material varied between 2 000 and 6 000 rad and the total treatment period from 14 to 28 days When teleradium (5 g cannon) was applied the daily dose usually amounted to 732 rad to each field of 28 26 cm at 6 cm distance 3 to 4 fields were employed Teleradium was mainly used for treating the nasopharynx and tonsils Telecobalt treatment with a daily skin dose mostly of 300 rad and a focus-skin distance of 60 to 80 cm was given 6 times weekly The treatment area was confined to the tumour and to its immediate environment No prophylactic irradiation was applied The treatment was administered to forty-one cases postoperatively after excision of the primary tumour Chemotherapy was included in three instances

The survival rate was calculated from the start of treatment

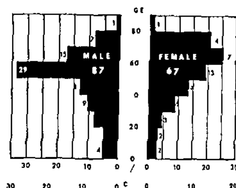


Fig. 1. Sex and age distribution in the series of 154 cases of reticulum cell sarcoma.

made in connection with the assessment of a recurrence or of a growth at a new site, the diagnosis then being based on the clinical signs. Lymphography was not yet in use at that time. In considering the mode of dissemination, data from the case histories were taken into account if consistent with the clinical signs.

The primary localization was considered to be the site at which the local disease was first diagnosed. Any new manifestation in an area already treated was considered to constitute a recurrence. Secondary occurrences were understood to be new areas of malignancy including those in the same region as the primary tumour but separate from the one treated. The secondary occurrences are presented according to a grouping by phases that indicate the chronologic order in which such occurrences were noted in each individual.

The age and sex distribution of the material are presented in Fig. 1. There were 87 men and 67 women, the male female ratio thus being 1.3:1. The peak frequency occurs in the 50—60 year age group of men and in the 60—70 year age group of women. The higher incidence of the disease in the younger age groups of men is evident from the figures.

The primary localizations in the present material are recorded in Fig. 2, five patients, in whom the disease was in the generalized stage on admission for treatment, being excluded. The disease commenced in the region of the head and neck in 88 cases (57 %) and in 85 of them (55 % of the material) the primary tumour arose in the lymphatic tissue in the cervical region.

The degree of spread of the disease was classified in three groups according to PETERS (1963).

Stage I — Single lymph node region or single site in extranodal tissue.

Stage II — Multiple lymph node regions, or single extranodal site with involvement of adjacent lymphatic region,

Stage III — Evidence of systemic disease, or involvement of the liver, spleen or bone marrow or a single extranodal site with involvement of remote lymphatic region.

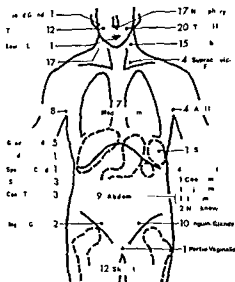


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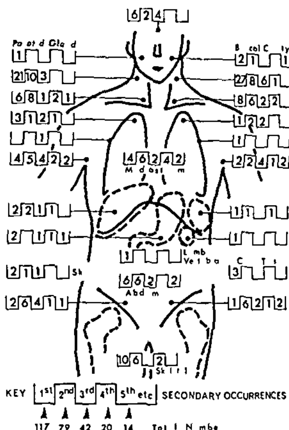
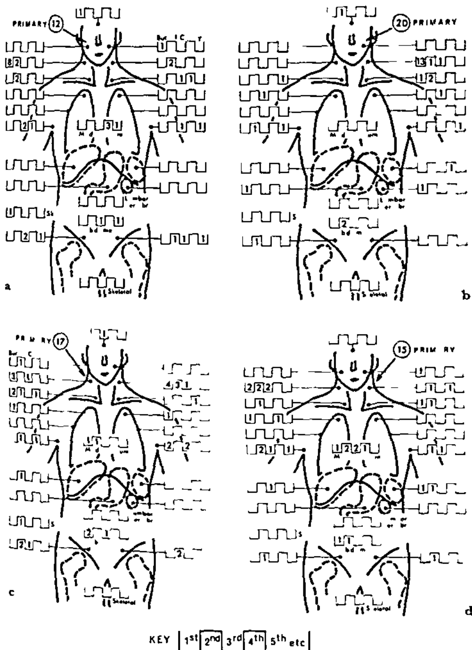


Fig 3 Sites of 272 secondaries in 111 cases of the series

Occurrence of secondaries Secondaries occurred in 127 of the 154 cases of the material (82 %) The sites totalled 272, or an average of 2 5 per case These locations, and the sequence in which they were established, are presented in Fig 3 The study was particularly directed towards an analysis of the occurrence of secondaries following a primary tumour of the tonsils, nasopharynx or region of the neck

A primary tonsillar location was established in thirty two cases, in twenty seven of which secondary tumours occurred The sixty seven sites of secondaries, thirty eight of which (57 %) were above the level of the clavicles, are given in Fig 4, a and b Twenty four of the first phase secondaries lay above the level of the clavicles and only three below it, namely one each in the stomach and kidney and one in the skin of the abdomen The proportional share of sites below this level increased in the later phases The most common sites were the axillae (8), groins (7) and mediastinum (4)

A primary nasopharyngeal tumour was present in seventeen cases (Fig 5) Forty seven secondaries were recorded in fifteeen cases, thirty (64 %) of these lay above the clavicles A single secondary in the first phase was observed below



SECONDARY OCCURRENCES

Fig 4 Secondaries at different sites *Upper left* in eleven out of twelve cases of primary tumour of the right tonsil *Upper right* in sixteen out of twenty cases of primary tumour of the left tonsil *Lower left* in sixteen out of seventeen cases of right primary cervical tumour *Lower right* in eight out of fifteen cases of left primary cervical tumour

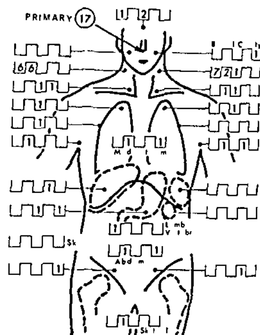


Fig 5 Secondaries in fifteen out of seventeen cases of primary nasopharyngeal tumour (See key in fig 4)

the level of the clavicles in a lumbar vertebra, whereas fourteen were located above this level *In the second phase, too, there were still nine supraclavicular and* only five infraclavicular sites The latter increased in relative number at the subsequent phases No preferential locations were noted among those below the level of the clavicles, three of which occurred in the axilla, two each in the mediastinum, groin, abdomen and lungs, and one each in the pleura, bones and liver

Of the thirty two cases with primary site of tumour in the neck, twenty four developed further growths (Fig 4, c and d) Six of these consisted of local recurrences while new locations numbered sixty six Of the secondary growths, forty one (57 %) lay below the level of the clavicles and half of this number in the adjacent lymph gland areas, namely, twelve in the axillae and eight in the mediastinum The site of the secondaries was supraclavicular and infraclavicular in thirteen and eleven cases, respectively, in the first phase, and in ten and seventeen cases in the second phase

The primary growth was situated in the skeleton in twelve cases, in nine of which the disease recurred Five of the secondaries (56 %) appeared in the bones In contrast, only fourteen secondaries were associated with 118 non skeletal primary tumours (12 %)

As regards the relation in time of the secondaries to the primary tumours in the preceding groups it was observed that regional secondaries appeared within 2 to 6 months in a considerable number of cases No distinct relationship

seemed to exist between the time preceding the appearance of secondaries and the prognosis. On the other hand secondaries at a more remote site usually preceded rapid deterioration even when such an occurrence did not follow for some time

Results

The survival rate in the total series is presented in Fig 6 Those surviving for one year or longer after demonstration of the primary tumour form 50 % of the series The survival rates after 2 5 and 10 years were 27 % 17 % and 9 % of all patients respectively The corresponding figures can also be read from the graphs presented for the groups in different clinical phases of the disease The stage on admission for treatment had a distinct influence on the survival The same is true in respect to the age of patients on admission (Fig 7) the prognosis deteriorated with increasing age Patients under 40 years constitute an exception to this in that their survival rate graph was nearly identical to that of those aged 60 to 70 years (5 year survival less than 15 %) This poor prognosis of patients under 40 is even more marked in the female age groups where the graph of those aged 60 to 70 on admission roughly approximates that for the patients who were 40 to 50 and 50 to 60 years old when treatment was undertaken for the primary growth

Fig 8 gives the survival rates in the groups with different primary tumour sites The most favourable 5 year results were in the groups of tonsillar mediastinal and abdominal primary tumours (20 % or better) The survival rate was poorest in the group with primary skeletal growths 25 % after 2 and zero after 5 years

The results of treatment in relation to the amount of radiation employed are seen in Fig 9 which indicates that the tumour dose of 3 000 rad over 3 weeks constitutes a limit below this the survival rates are obviously lower than the rates obtained when higher dose levels were the rule whereas virtually no differences were recorded between the groups of patients who received 3 000 to 5 000 rad and more than 5 000 rad respectively

Of the 14 patients who survived for 10 years or longer the site of the primary tumour was tonsillar in four nasopharynx in one neck in four axillar in two retroperitoneal glands in two and inguinal gland in one In seven of these no secondaries were noted while the other seven were later treated for neoplasms As an example of the last mentioned a male patient aged 55 years with a primary tumour of the neck was treated with irradiation up to 5 500 rad Secondaries subsequently necessitated treatment of the left axilla ad 4 000 rad the left

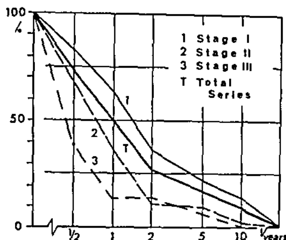


Fig 6 *Survival rates in the total series*

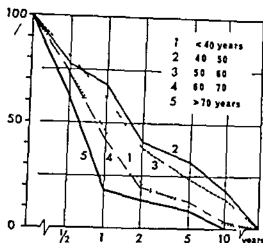


Fig 7 Survival rates in the different age groups of the series

pulmonary hilum ad 5 000 rad, both inguinal folds ad 5 000 rad, a recurrence in the left axilla ad 4 000 rad and the left parotid area ad 4 000 rad The patient was then symptom free for 8 years

Discussion

Reticulum cell sarcoma is a disease of late middle age, with peak incidence in male patients aged 50 to 60 and in female patients aged 60 to 70 years A higher frequency of onset of the disease in the younger age groups occurs in men The male female ratio was 1 3 1, which is consistent with other reports (e g BERGSTEINOVA et coll 1967)

Of the primary growths 57 % arose in the region of the head and neck This agrees approximately with other reports (GYENES 1967 with 50 % per cent, SCHEER 1963 with 62 %) BONADONNA et coll (1967) found 53% of the primary tumours within Waldeyer s ring, whereas in the present series the contribution of the tonsils and nasopharynx amounted to 31 %

Regarding other locations, i e sites below the level of the clavicles, remarkably *uniform distribution of the primary growths, without any indication of predilec* tions was noted The same observation applies to other series reported (SCHEER 1963 GYENES 1967)

Of the secondaries following a primary growth of the tonsils nasopharynx or cervical region, 59 % in all arose above the level of the clavicles Of the ton sillar, nasopharyngeal and cervical tumours, 89 % 93 % and 54 % respectively, produced first phase secondaries at supraclavicular site (50 % in SCHEER s series

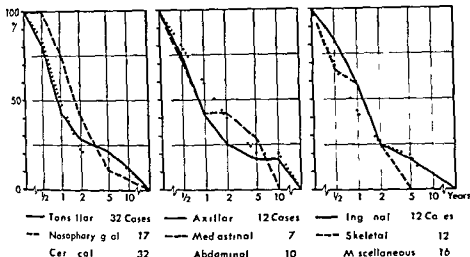


Fig 8 Survival rates in reticulum cell sarcoma at different primary sites

of primary tumours in the cervical region) Late secondaries below the level of the clavicles are widely dispersed with a predilection however for the axillae and mediastinum

Primary reticulum cell sarcomas of bone also display a distinct tendency to produce econdaries at skeletal sites (in 56 % of cases) as against only 12 % when the primary is in any other location

A comparison of the results of treatment against other series reported on the bas s of the 5 year survival rates is presented below

Bergsteinova et coll (1967)	49 cases	34 6 per cent
Molander & Pack (1965)		21 3
Cook et coll (1960)	94	21 2
Gyenes (1967)	40	20
Peters (1963)	73	16
Rosenberg et coll (1961)	534	13 9
Jacobs & Marasso (1964)	26	7 7
Present series (1969)	154	17

It would appear that the 5 year results in the present series are in the same order of magnitude as in many of the other series reported The 50 % mortality noted during the first year also confirmed previous observations (Peters Bergsteinova et coll Cook et coll)

The tumour dose of 3 000 rad over 3 weeks established as a significant limit from the results is in keeping with other series as well According to Gyenes

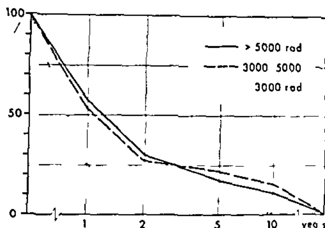


Fig 9 Survival rates in groups of the series treated at different radiotherapeutic dose levels

(1967), the frequency of recurrence was clearly higher among those who received less than 3 000 rad, his doses varied between 3 000 and 4 000 rad Similarly, JACOBS et coll (1964) recommended doses of 3 000 rad and higher PETERS (1963) suggested 5 000 rad over 4 weeks, she used between 4 000 and 6 500 rad BERGSTEINOVA et coll (1967) stated that they applied a method in which following disappearance of the tumour 50 % of the dose thus far administered was given HOLME & KUNKLER (1961) gave 3 000 rad over 4 weeks and FULLER & FLETCHER (1962) 5 000 rad with a 750 rad weekly dosage with orthovoltage and 1 000 rad per week with supervoltage therapy The various recommendations made in the literature may be summarized to the effect that most authors use a total dose of 4 000 to 5 000 rad This is in agreement with the experience of the present writers

Divergent opinions have been expressed concerning prophylactic irradiation Most authors consider there is no advantage to be gained by prophylactic irradiation of unaffected lymph gland regions (PETERS 1963, BERGSTEINOVA et coll 1967, SCHEER 1963) PARKER (1968) believed that as long as the dissemination of lymphomas is not completely understood, the primary regions and regional lymph regions should be treated EASSON (1967) has also recommended prophylactic irradiation similar to that in Hodgkin s disease

BONADONNA et coll (1967) considered prophylactic irradiation to be indicated only in connection with primary tumours established within Waldeyer s ring The present series suggests it wise to treat the entire cervical region prophylactically in reticulum cell sarcoma of the tonsils or nasopharynx On the other hand, prophylactic treatment of the axillae and mediastinum does not appear suitable in primary tumours of the cervical region, as SCHEER (1963) has pointed out The same is also obviously true for other primary locations, particular attention at follow up examinations should be paid to all lymph gland areas, and not only

to the probably affected areas The possibility of secondaries in tissues other than the lymphatic system should be kept in mind

Conclusions

1 The primary locations of reticulum cell sarcoma are above the level of the clavicles in more than half of cases

2 Secondaries occurred in 83 % of the cases with tonsillar and nasopharyngeal primary growths with only few exceptions the first secondaries occurred (89 % and 93 % of cases respectively) in the neck These primary locations justify pro phylactic irradiation of the entire cervical region prophylactic radiotherapy does not appear suitable when the primary growth is elsewhere

3 The tumour is locally curable with the comparatively large total dose of 4 000 to 5 000 rad over 4 to 5 weeks The reaction of the tumour to irradiation should be followed and the total dose adjusted accordingly

4 The course of the disease is remarkably malignant half of the patients dying within the first year The authors agree with the reports in the literature, however, that even good treatment results may be achieved in certain instances an inducement to endeavours to find the optimum therapeutic technique Mega voltage therapy would appear to offer considerable possibilities in this direction

Acknowledgement

The authors take this opportunity to thank Docent P Holsti who confirmed the pathology where necessary The study was aided by a grant from the Sigrid Jusélius Foundation

SUMMARY

The treatment results and spread of the tumour in 154 cases of reticulum cell sarcoma treated during the period 1951—1962 have been analyzed Particular attention was paid to the largest groups i e those with nasopharyngeal tonsillar and cervical primary location of the tumour Prophylactic irradiation of the entire cervical region is discussed

ZUSAMMENFASSUNG

Strahlenbehandlungsresultate und Ausbreitung der Tumoren wurden in 154 Fallen von Retikulumsarkom wahrend der Periode 1951—1962 analysiert Besonders wurden die grossten Gruppen beobachtet d h in denen die Tumoren im Nasopharynx, in den Tonsillen und im Hals lokalisiert waren Der Wert der prophylaktischen Bestrahlung der ganzen Halsregion wird diskutiert

RÉSUMÉ

Les auteurs ont analysé les resultats du traitement et l'extension de la tumeur dans 154 cas de sarcome a cellules reticulaires traites pendant la période 1951—1967. Ils ont preté une attention particuliere aux groupes les plus nombreux c'est a dire ceux des localisations primitives nasopharyngees amygdaliennes et cervicales. Ils etudient la valeur de l'irradiation prophylactique de toute la région cervicale

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FROM THE RADIOTHERAPY CLINIC OF THE CENTRAL HOSPITAL OF THE UNIVERSITY OF TURKU FINLAND

LARGE DIMENSIONAL MULTIFOCUS RADIATION SOURCE IN SUBCUTANEOUS SIEVE THERAPY

by

P KLAMI and P RUOTSALAINEN

A tumour surrounded by healthy tissue can be destroyed if the difference between the biologic effect of irradiation of healthy and pathologic tissue is sufficiently great With little or no difference the matter becomes a physical one of arresting the growth with as large a dose as possible without causing irreversible damage to the surrounding healthy tissues

A typical example is radiotherapy of subcutaneous tumours Healthy tissue is so close to the pathologic tissue that a sufficiently large dose difference cannot be obtained by physical means One way is to remove the skin surgically from the therapy field for a single irradiation If operation is to be avoided or fractionated therapy is preferred to one large single dose a high skin dose has to be given with disregard to tolerance As early as in the first half of this century KOHLER (1912) to avoid defects of this kind proposed the method known as Siebbestrahlung or sieve therapy which has been generally adopted for the treatment of deep-lying tumours

It is possible to give much higher doses to very small skin fields than to large skin fields because the former will recover A single field 1 cm in size can be

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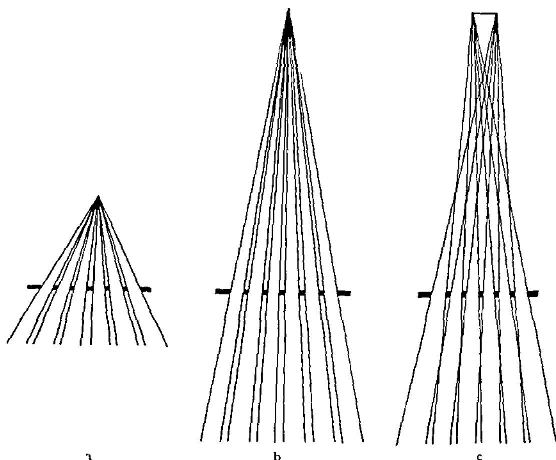


Fig. 1. Irradiation of an object through a sieve plate. The beams from a point source diverge more and more the deeper they penetrate the object (a), a fault somewhat reduced by a larger SSD (b). With a large radiation focus the edges of the penumbras begin to intersect (c).

irradiated to 35 000 rad or even to 50 000 rad without irreversible damage. The surrounding skin will remain unirradiated and regeneration can take place. This fundamental advantage is utilized in sieve therapy, larger areas being irradiated through the holes of the lead grid while the skin between the holes is protected from radiation (BARTH 1959).

Therapy of this kind is nowadays in use in many radiotherapy centers, although in principle the method embodies a considerable error. The primary beams from a point source through the holes of the sieve to an object, diverge further and further from each other the deeper they penetrate (Fig. 1a) and the dose distribution in the object becomes unhomogenous. Excepting secondary radiation, this disadvantage may be somewhat reduced by removing the source farther from the object (Fig. 1b). When the radiation focus is large the faint edges of the penumbra begin to intersect beneath the surface of the object.

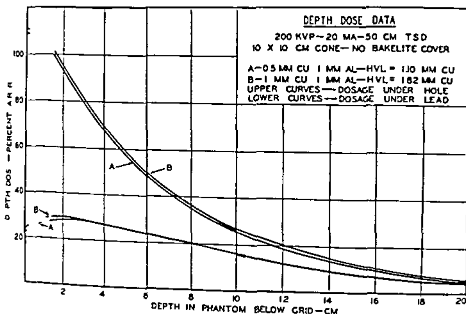


Fig 2 Depth dose in R per 100 R in air using a 10 cm × 10 cm cone without cover (From SOPP & STANTON Amer J Roentgenol 71 (1954) p 842)

The result produced by effectively penetrating roentgen rays (HVL 1 10 to 1 82 mm Cu SSD 50 cm) is presented in Fig 2 (SOPP & STANTON 1954) The dose distribution close to the skin is unhomogenous less so beneath the lead than beneath the holes (Fig 3 SOPP & STANTON) The dose differences are not satisfactorily equalized under less than a depth of about 14 cm in the tissue (difference < 30 %) The depth dose is thus only a little more than 10 % of the skin dose and the therapy is almost meaningless even with a skin dose as high as 20 000 rad

The sieve method used today could be much improved with a radiation source so arranged that one focus is provided for each hole of the grid (Fig 4a) The separated radiation beams would intersect still closer to the surface of the object if in addition the source of radiation could be brought close to the grid (Fig 4b) The use of a radiation source with large foci would offer still greater advantages (Fig 4c)

Radiologists working with the usual sources of radiation argue that in accordance with the inverse square law the intensity of radiation will rapidly fall off when the source of radiation lies so close to the object One of the authors of

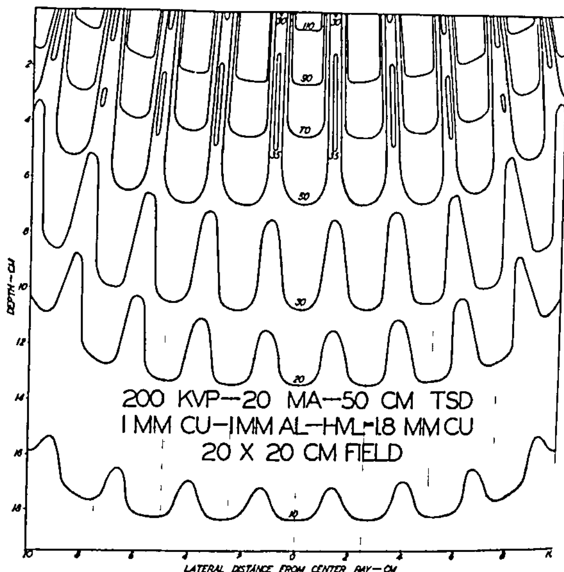


Fig. 3. Isodose curve for a 20 cm × 20 cm cone with bakelite cover. (From SOPP & STANTON: Amer. J. Roentgenol. 71 (1954) p. 844.)

this paper (KLAMI 1968) has earlier dealt with the theory of radiation sources of large area dimensions with every focus of the source delivering a collimated radiation beam. It seems that this kind of source differs from other known sources in that the relative depth dose is practically independent of the focus-skin distance. This is explained by the fact that the sum effect of separated radiation beams increase in proportion to the square of the distance, which thus is an effect opposite to the inverse square law. Accordingly, a source of radiation of

a b c

Fig 4 Irradiation of an object through a sieve plate from a multifocus radiation source (a) The beams intersect nearer the object surface when the source skin distance is short (b) an advantage which is increased by a large focus (c)

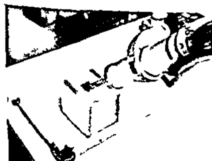


Fig 5 Arrangement for experiment A multi focus r diation source s simulated by gradually

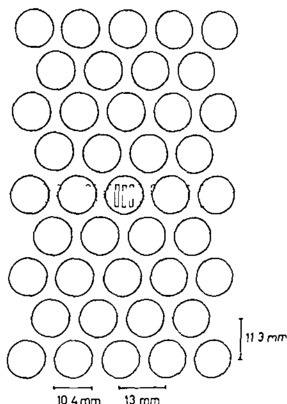


Fig 6 The positions of the radiation focus during the experiment A row of LiF teflon microrods for measuring the homogeneity of the field at 1 cm lie in the middle

this kind when used for sieve therapy may be brought extremely close to the object and sieve by taking into account the nature of the source, without debasing the relative depth dose The dose will decrease only due to absorption and scattering in the object Thus, when the focus skin distance becomes less, the relative depth dose will also decrease because the area of the skin field in every separated radiation beam will grow smaller Some other insignificant sources of error will also be present in the calculations and demand that the applicability of this sieve therapy method be checked empirically

A multifocus tube has not yet been built because its advantages have not been recognized It is possible however to examine the applicability by simulating such a tube (Fig 5) A conventional slope target tube has been used as the source of radiation so that the target could be brought quite close to the object A sheet of lead with a hole equal in size to that of the grid was set in front of the source of radiation A lucite phantom was moved step by step in relation to the stationary hole of the grid so that the irradiation beam was brought in turn to the positions in Fig 6 and the irradiation time through every hole was of the same length

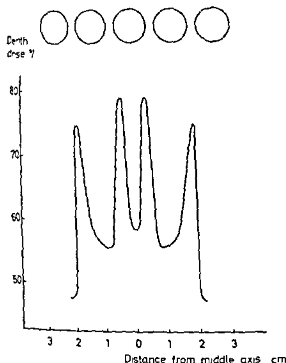


Fig 7 The appearance of the depth dose curve at the depth of 1 cm measured as shown in Fig 6

Measurements were carried out on the lucite phantom which was composed of 1 cm plates 15 cm × 15 cm in size Lucite was selected because its absorption properties correspond to water Slots were cut for three LiF teflon microrods (diameter 1 mm and 6 mm long) side by side at 1 mm distances for measuring the depth dose on each plate The empty space was filled with water A whole row of slots were also cut for the microrods beneath the middle row of the holes of the grid for measuring the homogeneity of the radiation field at a depth of 1 cm in that particular plate The distance between these slots was 2 mm Fig 6) The depth dose curve was measured only beneath the middle hole the doses were recorded with the Con Rad TLD Reading Instrument (RUOT SALAINEN)

The dose at 1 cm was well levelled and the doses beneath the lead strips were even higher than those beneath the holes (Fig 7) This was due to the edges of the beams from the various holes beginning to intersect at a depth of about 5 mm The measured percentage depth doses and technical data are presented in Fig 8 The half value layer in tissue (HVLT) is about 3 cm which is more than three times the HVLT of usual contact therapy with the same HVL and SSD

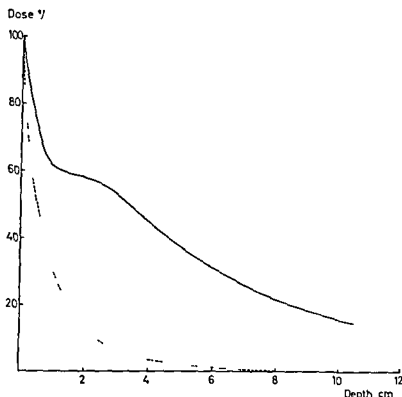


Fig 8 The relative depth dose achieved in the experiment in fig 6 (unbroken line) compared with that in conventional irradiation through one hole (dashed line) Technical data in both cases 100 kV 0 3 mm Cu SSD 15 mm

Discussion

The purpose of this preliminary investigation has been to examine the possibilities presented by this new kind of sieve therapy The experiment reported is one of many others along the same lines Many details, such as the best ratio of the grid and the shape of the holes, have yet to be investigated It has also not been decided whether the skin recovers as well as it does after conventional sieve therapy

If the aim were to give 6 000 rad to a tumour, and 20 000 rad could be applied to the skin, the tumour dose mentioned above would be reached at a depth of about 6 3 cm with a tube voltage of 100 kV The HVLT could be increased by raising the energy of radiation although this would demand roentgen rays produced by low energy accelerators and consequently more expensive apparatus But with higher energies of 0 2 MeV or more the differences between the absorption in various tissues would be equalized, e g it would be possible to irradiate the chest wall radically

SUMMARY

Phantom experiments have suggested that the best object for sieve therapy is the subcutaneous tumour that can be radically irradiated by using a large dimensional radiation source and a short source skin distance. The theory is discussed in detail.

ZUSAMMENFASSUNG

Phantomexperimente zeigten, dass das am besten geeignete Objekt für die Siebbestrahlung ein subkutan gelegener Tumor ist, der radikal von einer Strahlenquelle grossen Durchmessers und mit kurzem Hautabstand bestrahlt werden kann. Die theoretischen Bedingungen werden erörtert.

RÉSUMÉ

Des expériences sur fantomes ont montré que le meilleur objet pour thérapie suivant la méthode du crible est une tumeur sous-cutanée qui peut être irradiée radicalement par une source de radiation de grande dimension avec une courte distance source peau. Les auteurs discutent en detail la théorie de cette méthode.

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FROM THE DEPARTMENTS OF RADIOLOGY OF THE ST EUGENIO HOSPITAL AND THE ST GALLICANO INSTITUTE OF DERMATOLOGY, ROME, ITALY

LATERALLY SCATTERED RADIATION USED IN SUPERFICIAL ROENTGEN THERAPY

by

P L BARBIERI, S MAZZOLA and F SABATINI

The investigation was performed to determine whether radiation scattered by the Compton effect from a block hit by an unfiltered beam from a conventional roentgen apparatus possesses such characteristics of intensity and distribution of dose as to be usefully employed in superficial roentgen therapy

Contact therapy satisfies this condition because it produces a rapid fall in the depth dose and therefore the possibility of achieving a high dose to the first millimetres of tissue with very low damage of the underlying tissues The problem was however to see whether the same objective could be obtained with a conventional roentgen equipment The distribution of an isodose chart suggested that the radiation from a scattering block mounted in a conventional roentgen therapy applicator *with a lateral window on one of its sides could be utilized for* the purpose

In one of the charts of TSIEN & COHEN (1962) of an object irradiated at FSD 50 cm *with 1 mm Cu filter other curves laterally appear to correspond* to the isodose curves of the principal beam Two graphs are given in Fig 1, the first with a value of 10 % of the incident dose and the second with 5 %, i e half of

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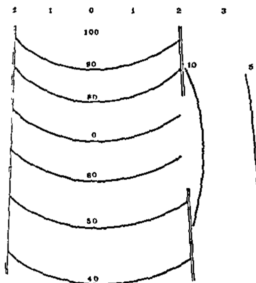


Fig 1 Isodose chart from TSIEN & COHEN (1962) with isodose curves of the main beam and corresponding lateral curves FSD 1 mm Cu The figures given at the top indicate the width of the beam in centimetres

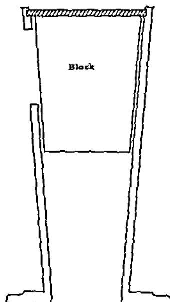


Fig 2 Lateral sectional view of a conventional roentgen therapy applicator with a block of low atomic weight material

the first and 1 cm of tissue in the intermediate space between the two lateral curves

Since our dosimetric measurements in air at a focus skin distance of 50 cm gave an output of 70 R/min and this figure was too low for our purpose the 1 mm Cu filter was eliminated and a much higher output 500 R/min was obtained

Various blocks of low atomic weight material (rice graphite wood and paraffin) were irradiated with the aid of a Victoreen chamber in a conventional roentgen therapy applicator Examination of the scattered radiation from the window in one of the sides of the applicator (see Fig 2) established the following facts

1 That a high incident exposure rate i e a sufficient lateral output to satisfy practical purposes necessitated a high output

2 For easy handling and setting the optimal FSD of the applicator was 40 cm

3 The exposure rate of the scattered radiation from a rice block hit by a 220 kV 15 mA beam measured at the center of the window was 40 R/min

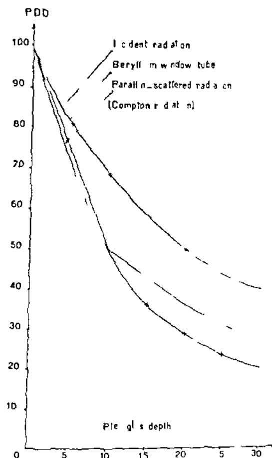


Fig 3 Percentage depth dose values in *plexiglas at various depths with a focus* skin distance of 30 cm and when using a low energy beam with HVL 1 mm Al a beryllium window tube with HVL 0 9 mm Al and paraffin scattered radiation ('Compton radiation') *with HVL* 2 mm Al

4 The optimal thickness of the block was 6 cm, and a greater thickness was of no advantage because of autofiltration phenomena

5 The HVL of the scattered radiation at the window was 2 mm Al

In this manner a soft, unfiltered radiation, very similar as regards dose distribution and proximity of the target to that of a circular radium source could be achieved

The exposure rate of the superficial radiation falls to 50 % after passing through 10 mm of plexiglas, to 36 % after 15 mm, to 23 % after 25 mm and to 20 % after passing through 30 mm of the material The gain is evident if it is compared with the output of a conventional roentgen beam of low energy (50 kV, FSD 30 *cm, HVL 1 mm Al*)

For a field of 4 cm × 4 cm, the measurements were 69 % at 10 mm 50 % at 20 mm, and at 30 mm the measurement was still 40 % of the superficial dose

In theory at least, better conditions are obtainable by this laterally scattered radiation, which may be termed Compton radiation, than with radiation pro-

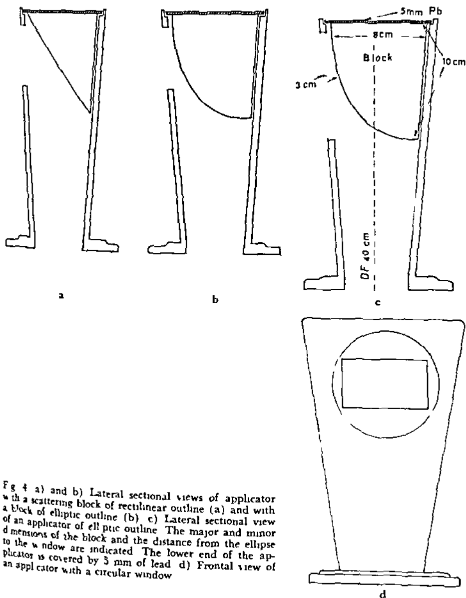


Fig 4 a) and b) Lateral sectional views of applicator with a scattering block of rectilinear outline (a) and with a block of elliptic outline (b) c) Lateral sectional view of an applicator of elliptic outline The major and minor dimensions of the block and the distance from the ellipse to the window are indicated The lower end of the applicator is covered by 5 mm of lead d) Frontal view of an applicator with a circular window

duced by beryllium window tubes (Fig 3) The final problem was to obtain incident radiation of an intensity to allow employment in practice and homogeneous from the centre to the periphery of the field

Paraffin is preferable to other materials (such as wood or rice) since it gives

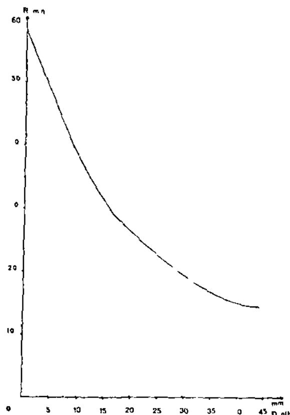


Fig 5 Output of Compton radiation with a plexiglas absorber (ordinate) at various depths using a paraffin block of elliptic outline and incident radiation from a 200 kV 18 mA beam

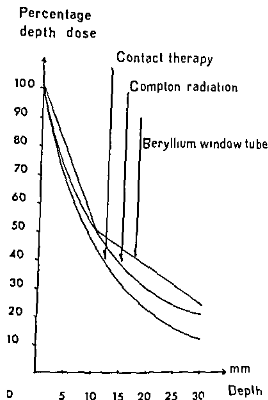


Fig 6 Percentage depth dose values in contact therapy FSD 2 5 cm F = 3 cm diameter and Compton radiation with 30 cm FSD at 50 kV and 20 mA and respectively with beryllium window tube

a high Compton effect and because of its lower autoabsorption and the ease with which it can be moulded The mould of the paraffin has to be such that the most uniform possible output at the window can be obtained Obviously, the applicator could not be entirely filled with paraffin, since the elements distal to the tube would have received already filtered radiation by reason of the partial absorption of the latter as it traverses the scattering block The surface of the block, which is the principal component from which the less absorbable Compton photons arise, had to be increased Mould of a scattering block, the outline of which is rectilinear, is depicted in Fig 4a It is evident that the centre is too far from the window

The output was better with a cylindrical mould although the spatial homogeneity was poor (Fig 4b) Experiments proved that a cylindric mould of elliptic cross-section was the most adequate and that the optimal dimensions were 10 cm for the major axis and 8 cm for the minor axis The ellipse had to be at a

distance of 3 cm from the window (Fig 4c) The window field in this first realization was circular, 10 cm in diameter, and into it could be inserted various lead applicators adaptable to the lesion to be treated (Figs 4b to 4d) The bottom of the applicator was closed with 5 mm of lead

Using the applicator shown in the previous figures, the Compton output of a 200 kV 18 mA unfiltered beam at the centre of the window was 58 R/min while at the periphery it was 54 R/min The output at various depths is recorded in Fig 5 At the surface it was 58 R/min at 10 mm it was 28 R/min at 15 mm it was 21.5 R/min and at 20 mm depth it was 17 5 R/min

A comparison of the fall in percentage depth dose of the Compton radiation in relation to contact therapy and beryllium window tubes indicated that it was slightly lower than the first and little higher than the second The variation between the centre and the periphery is much more noticeable with the Philips contact therapy unit in a field of 4 5 cm diameter and 5 cm FSD it reached 40 %

Compton radiation thus appears to offer the advantage of allowing larger fields to be used and a better uniformity of dose distribution (Fig 6)

Palmieri (1923) described a roentgen therapy method similar to the one now presented A few years later Mainoldi published details regarding the experimental biologic basis of the method These papers exploit not only the Compton effect of a block in an applicator but the main beam as well The physical principle is based on the use for therapeutic purposes of the most penetrating radiation from the block emerging from the bottom of the applicator

Conclusions

It thus appears that Compton radiation laterally scattered from a block of paraffin in a conventional roentgen therapy applicator can be used in superficial roentgen therapy treatment The low percentage depth dose in tissue is due to the Compton effect the proximity of the radiation centres and absence of the intermediate glass walls that are present in conventional roentgen tubes A study of the macroscopic and microscopic alterations produced in the skin of laboratory animals by scattered radiation has just been completed and will be published shortly

Acknowledgement

The authors wish to thank Mr Plinio Fantoni Ph D for his helpful advice and assistance in the physical experiments

SUMMARY

A new roentgen therapy method based on laterally scattered radiation is described. The low percentage depth dose and uniformity of distribution are due, among other things, to the Compton effect. The method should prove valuable in superficial roentgen therapy.

ZUSAMMENFASSUNG

Eine neue Bestrahlungsmethode wird vorgeschlagen, bei der die seitliche Streustrahlung benutzt wird. Die geringe prozentuale Tiefendose und die ebenmässige Verteilung beruhen neben anderen Umständen auf dem Compton-Effekt. Die Methode ist besonders für die Oberflächenbestrahlung von Nutzen.

RÉSUMÉ

Les auteurs décrivent une nouvelle méthode de roentgenthérapie basée sur l'utilisation du rayonnement diffusé latéralement. Le faible pourcentage de dose en profondeur et l'uniformité de la distribution sont dus, entre autres choses, à l'effet Compton. Cette méthode devrait être utile en roentgenthérapie superficielle.

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CLINICAL COURSE OF HODGKIN S DISEASE TREATED WITH RADIOTHERAPY

by

TORSTEN LANDBERG

The prognosis in Hodgkin s disease has long been regarded as gloomy It has for instance been claimed that bisher durch Strahlenbehandlung nennenswerte Heilerfolge nicht erreicht werden konnen (BAENSCH 1936) that Hodgkin s disease is in the end always fatal (PATERSON & PATERSON 1954) and that only prolongation of life can be expected (ACKERMAN & DEL REGATO 1962)

According to recent literature however the disease may often be initially local (CRAVER 1954 HEALY et coll 1955 SLAUGHTER et coll 1958 KAPLAN 1962 1966 EASSON & RUSSEL 1963 and PETERS 1966) Long survivals without signs of disease have been reported after surgery (SLAUGHTER et coll) or radiotherapy (GILBERT & BABAIANTZ 1931 PETERS 1950 GILBERT 1956 PETERS & MIDDLEMISS 1958 KAPLAN EASSON & RUSSEL, JELLIFFE 1965) It has been argued that reports of permanent cures should be viewed with scepticism since long remissions are not uncommon (MERNER & STENSTROM 1947 ACKERMAN & DEL REGATO) According to EASSON & RUSSEL a realistic meaning however can be given to the word cure if cure is taken to connote that in time — probably a decade or two after treatment — there remains a group of disease free survivors

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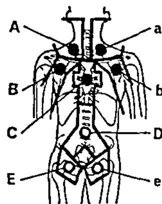


Fig 1 Diagram of distribution of some large lymph node groups
A a — cervical and supraclavicular
B b — axillary
C — mediastinal
D — para aortic and para iliac regions
E-e — inguinal

whose annual death rate from all causes is similar to that of a normal population group of the same sex and age distribution and such groups of patients have been reported (EASSON & RUSSEL, EASSON 1966, KAPLAN 1966, MUSSHOFF & BOUTIS 1967) The possibility of a permanent cure of Hodgkin s disease has also been stressed by KAPLAN (1962) and JELLIFFE (1965)

Though some patients with clinically local disease seem to recover, many later develop fatal manifestations The clinical picture of Hodgkin s disease is dominated by involvement of certain lymph node groups, particularly in the neck, supraclavicular fossa, axilla, mediastinum, retroperitoneum and the groin (Fig 1) The disease usually first appears at one of these sites (SLAUGHTER & CRAVER 1942, PETERS 1950, NICE & STENSTROM 1954, WESTLING 1965, ULTMANN 1966 and MUSSHOFF et coll 1966) Classification of the lymph nodes in different groups is purely topographical for no sharp anatomic borderlines seem to exist though the thoracic duct is a short cut between the abdomen and the supraclavicular fossa (ROSENBERG & KAPLAN 1966) It has long been held that it *is not possible to predict the sites of later manifestations* (MERNER & STENSTROM, NICE & STENSTROM SCHEER 1963) which implies a policy to irradiate only clinically involved lymph node groups It has however, been postulated that the disease has a tendency to progress along the lymphatic pathways (JELLIFFE 1965, NEWALL 1965, KAPLAN 1966 ROSENBERG & KAPLAN 1966, PETERS 1966 and LANDBERG & LARSSON 1968) and to spread by extension per continuitatem (ACKERMAN & DEL REGATO) It has been suggested that Hodgkin s disease remains confined to the lymphatic tissues for a variable, but often considerable period of time before true generalization occurs (ROSENBERG & KAPLAN) The methods available for demonstrating involvement of deep lymph nodes are not satisfactory Routine examination will sometimes miss early changes in the mediastinum (FISHER et coll 1962 RUBIN & KUROHARA 1966, ROSENBERG & KAPLAN 1966), and if the examination does not include lymphography a retro-

Table 1

Localization of first extension in local Hodgkin's disease

Authors	Total number of patients	In a group adjacent to original site	At distant sites
PETERS (1950)		With few exceptions	
CROSBIE (1962)	42	15 (17)	19
SCHEER (1963)	68	21	
NEWALL (1965)	36	20	16
JELLIFFE (1965)	18	12	6
ROSENBERG & KAPLAN (1966)	90	22	4
LANDBERG & LARSSON (1968)	23	13	3

peritoneal lymphoma may remain concealed for a long time before it is detected (LEE et coll 1964 COOK et coll 1966 and ULTMANN 1966) It is also difficult to chart the spread of the disease to superficial lymph nodes SLAUGHTER et coll (1958) demonstrated that in operative specimens from the neck enlarged lymph nodes are sometimes surrounded by small but nevertheless changed lymph nodes Since local lesions can usually be readily controlled by radiation (JELLIFFE 1965 NEWALL 1965 and KAPLAN 1966) in cases where only clinically involved lymph nodes are irradiated any new manifestations will as expected often first appear in adjacent lymph node groups (Table 1) The word adjacent is seldom defined but EASSON & RUSSEL (1963) SCHEER (1963) and KAPLAN (1966) did not consider the lymph nodes in the axilla on one side and in the neck/axilla on the other as adjacent EASSON & RUSSEL (1963) did not regard the lymph nodes in one groin as adjacent to those on the opposite side but there is a direct lymphatic communication between the two groins at least when blockage of nodes has caused retrograde flow (FUCHS 1965 and WILJASALO 1965) The two inguinal groups were considered adjacent by HANCOCK & LEDLIE (1967) who have given some examples of adjacent groups Good results have been obtained after irradiation of not only clinically involved lymph node groups but also of adjacent clinically uninvolved groups (PETERS 1950 1966 PETERS & MIDDLEMISS 1958 KAPLAN 1962 1966 SALZMAN et coll 1964 JELLIFFE 1965) Whether such prophylactic irradiation of clinically uninvolved lymph node groups has any true effect on the further course of the disease is not clear (NEWALL 1965 EASSON 1966 RUBIN & KUROHARA 1966) and SCHEER questioned whether such treatment is rational

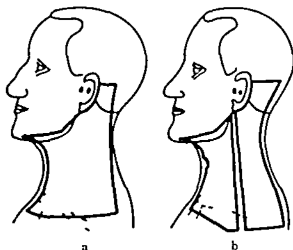


Fig 2 Standard treatment of neck and supraclavicular fossa (170 kV 0.9 mm Cu HVL 60 cm FSD) a) One field perpendicular to the side of the neck b) One ventral and one dorsal tangential field

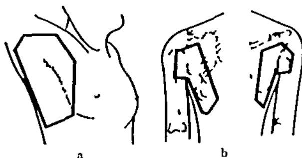


Fig 3 Standard treatment of axilla (170 kV 0.9 mm Cu HVL 60 cm FSD) a) One field to upper part of axilla b) One ventral and one dorsal field

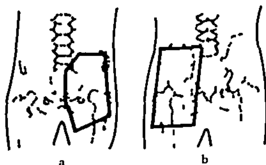


Fig 4 Standard treatment of groin (170 kV 0.9 mm Cu HVL 60 cm FSD) a) One ventral field b) One dorsal field

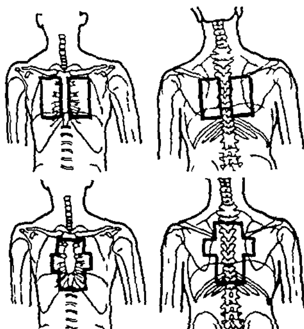


Fig 5 Standard treatment of mediastinum *Upper* oblique ventral and dorsal fields (170 kV 0 9 mm Cu HVL 60 cm FSD) *Lower* two opposed fields (^{60}Co 70 cm SSD)

This paper is concerned with a retrospective investigation of the clinical course of Hodgkin s disease treated with radiation

Clinical material and methods The material consisted of 149 patients (93 males and 56 females) admitted between 1944 and 1960 because of Hodgkin s disease and in whom re examination of histologic slides of lymph node biopsy specimens had verified the diagnosis These biopsies had been performed *before* any treatment had been started The age distribution is given below

Age in years	Number of patients	Age in years	Number of patients
<11	2	41—50	22
11—20	9	51—60	16
21—30	27	61—70	26
31—40	27	>70	20

Each patient was examined usually by two physicians before treatment The first examination included determination of Hb red cell count white cell count differential count platelet count ESR and microscopic examination of the urine Treatment had also been preceded by roentgenography of the chest

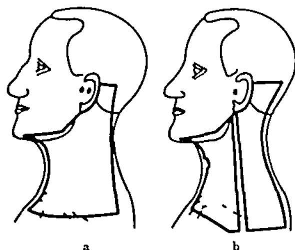


Fig 2 Standard treatment of neck and supraclavicular fossa (170 kV 0 9 mm Cu HVL 60 cm FSD) a) One field perpendicular to the side of the neck b) One ventral and one dorsal tangential field

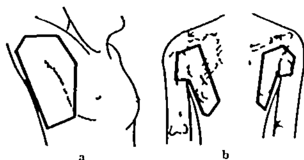


Fig 3 Standard treatment of axilla (170 kV 0 9 mm Cu HVL 60 cm FSD) a) One field to upper part of axilla b) One ventral and one dorsal field

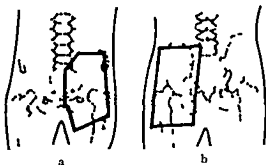


Fig 4 Standard treatment of groin (170 kV 0 9 mm Cu HVL 60 cm FSD) a) One ventral field b) One dorsal field

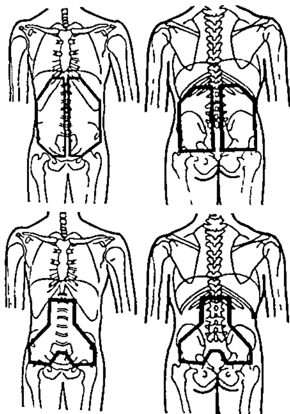


Fig 6 Standard treatment of para aortic and para iliac regions *Upper* oblique ventral and dorsal fields (170 kV 0 9 mm Cu HVL 60 cm FSD) *Lower* two opposed fields (^{60}Co 70 to 100 cm SSD)

Stage III Generalized lymph node involvement intra abdominal involvement involvement of structures other than lymphatic constitutional symptoms for which there was no other reasonable cause

The histologic classification was made according to the method of Lukes et coll (1966) The following histologic types were recognized lymphocytic predominance nodular sclerosis mixed cellularity and lymphocytic depletion (Landberg & Larsson 1969) The distribution of cases according to clinical stage and histologic type is recorded in Table 2

In accordance with the nomenclature suggested by Kaplan (1966) new manifestations in previously unirradiated areas were classified as extensions while the term recurrence was reserved for the re appearance of the disease at a site of treatment after an initial course of radiotherapy No attempt was made to differentiate between true and marginal recurrences or reseeding If a

Table 2

Distribution of material according to clinical stage (JELLIFFE & THOMSON *1955* JELLIFFE *1965*) *and histologic type* (LUKES *et coll* *1966*)

Histologic type	Clinical stage			
	I	II	III	Total
Lymphocytic predominance	9	8	1	18
Nodular sclerosis	4	16	11	31
Mixed cellularity	6	24	50	80
Lymphocytic depletion	2	2	16	20
	21	50	78	149

in 147 patients and by cavo urography in 11 patients In none was treatment preceded by lymphography

A total of 134 patients were treated primarily with radiation, which was initially combined with cytotoxic therapy in seven patients In twelve of the remaining fifteen patients treated primarily with cytotoxics, the disease was advanced, and ten of the fifteen later received radiation

Only the clinically affected lymph node groups were irradiated Lymph node groups A-a, B b, C, D, E e (see Fig 1) were irradiated according to standard techniques (Figs 2 to 6) The neck, supraclavicular fossa axilla and groin were treated with conventional roentgen rays with one or with two opposed portals Mediastinal and retroperitoneal lymphomas were given either conventional roentgen therapy with four oblique portals, or, in more recent years, with ^{60}Co with two opposed fields Treatment was usually given in the form of a split course with two-thirds of the total dose in the first series and the rest in the second series after a 5 week interval Treatment with conventional roentgen was usually administered with at most 3 500 R to each field, while in treatment with ^{60}Co the target dose usually consisted of 3 500 rad

The patients were regularly followed up at the department (LINDGREN 1962)

The grading in clinical stages was made according to the classification of JELLIFFE & THOMSON (1955) and JELLIFFE (1965), as indicated in the following paragraph

Stage I Lymph node involvement of only one main group, excluding intra abdominal disease

Stage II Lymph node involvement of two or more groups in the upper or lower half of the body excluding intra abdominal disease

Results and Discussion

Manifestations at first treatment The disease was classified as stage I in 21 patients (Fig 7) In only one of these patients (Case 138) were the affected lymph nodes situated below the level of the diaphragm

The disease was classified as stage II in 50 patients (Figs 8 and 9) Lymphoma was diagnosed in the popliteal fossa in one of these patients (Case 30) and changes in one tonsil were noted in another (Case 132) These changes were regarded as corresponding to groups E e and A a B-b C respectively In only two of the patients (Case 30 and 146) were the affected lymph nodes situated below the level of the diaphragm If the two groins were accepted as adjacent groups, the involvement of the lymph node groups could be considered continuous in forty-eight and discontinuous in two patients (Cases 26 and 152)

The disease was classified as stage III in 78 patients in 35 of whom one or more of the lymph node groups A a B-b C D E-e were involved but no other sites In six of these thirty five patients only one lymph node group was involved, namely in the abdomen in two in the neck in three and in the axilla in one The latter four patients were classified as stage III because of constitutional symptoms In eight of the thirty five patients the disease had involved two or more of the lymph node groups A a B b C D E e only above or below the diaphragm and in all the patients by continuity between the lymph node groups involved Also these eight patients were classified as stage III because of constitutional symptoms In three of the thirty five patients lymphoma was diagnosed only in the abdomen and in one groin while in the remaining eighteen patients lymph node groups on both sides of the diaphragm were affected In only one of these eighteen patients had all the affected lymph node groups been involved per continuitatem, the mediastinal lymph node group having been missed in one the abdominal group in one and the mediastinal and abdominal groups in fifteen patients In the remaining 43 of the 78 patients in stage III *other organs* were also involved viz the lung parenchyma in sixteen the spleen in ten the liver in nine the skin in nine the digestive tract in four the skeleton in three the mammary parenchyma in one the thymus in one and the oesophagus in one In thirty six of the forty three patients two or more of the lymph node groups were affected and in sixteen all the affected lymph node groups had been involved per continuitatem The mediastinal lymph node group had been missed in six the abdominal in four the mediastinal and abdominal in nine and the mediastinal or the cervical lymph node group in one patient

Thus in 106 (71 %) of the 149 patients organs (*Fig 10*) other than lymph node groups A a B-b C D E-e were not clinically involved at the time of

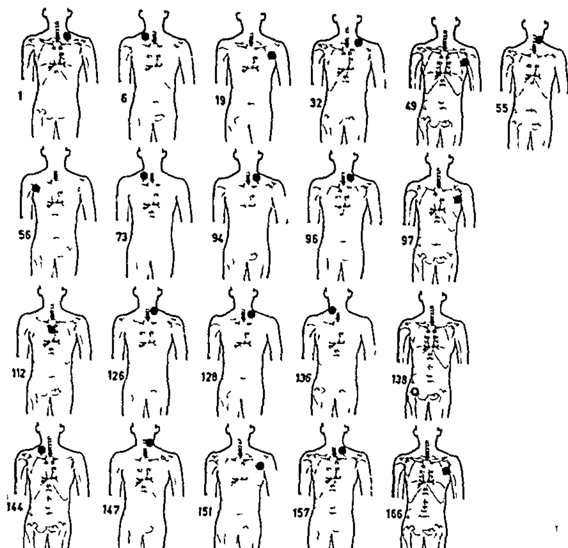


Fig 7 Histologic type (according to LUKES et coll 1966) in 21 patients in stage I Case Nos 1 — mixed cellularity 6 — nodular sclerosis 19 — lymphocytic depletion 32 and 49 — mixed cellularity 55 — lymphocytic depletion 56 — nodular sclerosis 73 and 94 — lymphocytic predominance 96 — mixed cellularity 97 — lymphocytic predominance 112 — nodular sclerosis 126 and 128 — lymphocytic predominance 136 and 138 — mixed cellularity 144 — lymphocytic depletion 147 and 151 — lymphocytic predominance 157 — nodular sclerosis 166 — lymphocytic predominance

month or more had elapsed betweeen the diagnosis of new manifestations they *were considered to have occurred at different times* The *duration of follow up* was calculated from the time of beginning of treatment whether it consisted of radiation or treatment with cytotoxics and concluded on 1 January 1966, i e a minimum possible follow up of 5 years

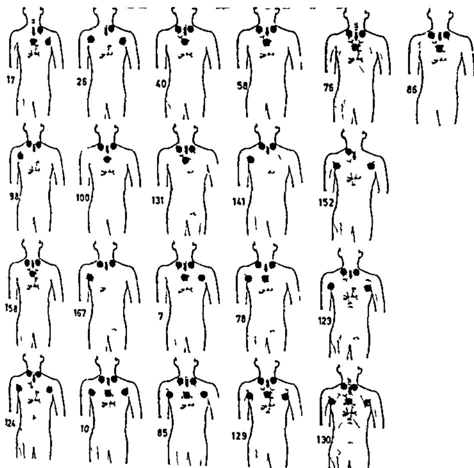


Fig 9 Histologic type (according to LUKES et coll 1966) in 21 patients in stage II with involvement of three or more lymph node groups Case Nos 17 and 26 — mixed cellularity 40 — nodular sclerosis 58 — mixed cellularity 76 and 86 — nodular sclerosis 98 — lymphocytic predominance 100 — *mixed* cellularity 131 — nodular sclerosis 141 152 and 158 — mixed cellularity 167 — nodular sclerosis 7 78 and 123 — mixed cellularity 124 lymphocytic predominance 10 and 85 — nodular sclerosis 129 — mixed cellularity 130 — nodular sclerosis

primary treatment The difference between these patients and the remaining 43 (29 %) was highly significant (at the 0 1 % level) In 27 of the 106 patients only one lymph node group was involved and of the remaining 79 patients the lymph node groups affected had been involved per continuitatem in sixty and per saltam in nineteen The high frequency of missed mediastinal and retroperitoneal lymph node groups might partly be explained by the difficulties in detect

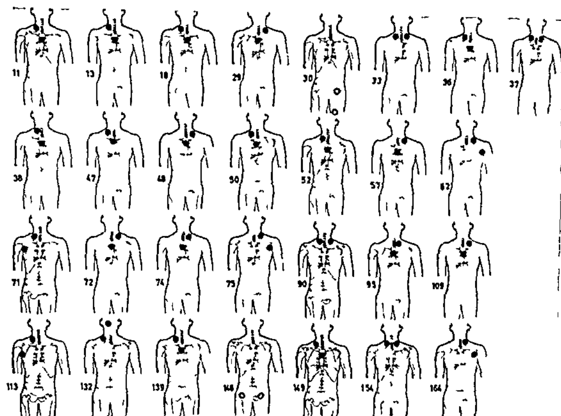


Fig 8 Histologic type (according to LUKES et coll 1966) in 29 patients in stage II with involvement of two lymph node groups Case Nos 11 — lymphocytic predominance 13 — nodular sclerosis 18 — lymphocytic predominance 29 and 30 — mixed cellularity 33 — lymphocytic depletion 36 and 37 — lymphocytic predominance 38 — nodular sclerosis 47 — lymphocytic predominance 48 — nodular sclerosis 50 52 and 57 — mixed cellularity 62 — lymphocytic predominance 71 — mixed cellularity 72 and 74 — nodular sclerosis 75 and 90 — mixed cellularity 95 nodular sclerosis 109 — mixed cellularity 113 — lymphocytic depletion 132 139 and 146 — mixed cellularity 149 — nodular sclerosis 154 — mixed cellularity 164 — nodular sclerosis

Table 3

Sites of first extensions in relation to the lesions diagnosed before treatment in 71 patients in stages I and II

	Number of patients		
	Stage I	Stage II	Total
No extensions noted	9	13	22
First extension			
In lymph node groups on the same side of diaphragm	6	15	21
In lymph node groups on the other side of the diaphragm	1	6	7
In lymph node groups on both sides of the diaphragm	2	2	4
In tissues outside the lymph node groups	1	10	11
In tissues outside the lymph node groups + in lymph node groups	2	4	6

ing pathologic lymphomas in these groups, especially *in the retroperitoneal group* when lymphography is not performed

Further course after primary treatment The crude 5 year survival rate was 6? % for stage I 48 % for stage II and 9 % for stage III (LANDBERG & LARSSON 1969) Of the patients in stage III, only 24 % were alive 2 years after the primary treatment compared with 76 % of those in stage I and 66 % of those in stage II

The study of the further clinical course after the beginning of treatment was confined to patients in stage I and stage II The duration of follow up and the time of detection of extensions and recurrences *in the lymph node groups* A a B-b C, D E-e as well as the first extension outside the lymph node groups are given in Fig 11 (stage I) and Fig 12 (stage II)

In 2? of the 71 patients (Table 3) no further clinical manifestations were diagnosed The sex distribution in these twenty two patients was the same as that of all patients in stage I and II thirteen patients are still alive In one of them (Case 85) all lymph node groups above the diaphragm had been involved before treatment in another (Case 146) the two groins, and in two patients (Cases 56 and 166) the axilla while the disease was confined to groups A a and C in eight and to A a and B in one patient (Case 167) Nine of the twenty two *patients in whom no further manifestations were diagnosed* died Autopsy was performed in four of these (Cases 136 141 78 and 124) and revealed no signs of Hodgkin s disease in one (Case 124) but residual foci in the remaining three patients One patient (Case 151) probably died from a generalized soft tissue sarcoma but also had advanced carcinoma of the thyroid and four patients (Cases 32 49 62 and 90) died at home three of these patients (Cases 32 62 and 90) were last seen at the department 5 months before they died Thus *irradiation of only clinically involved lymph node groups could initially have* cured at the most nineteen (27 %) of the seventy-one patients in stages I and II

Extensions were noted in 49 of the 71 patients in stages I and II (Figs 11 and 12 Table 3) The first extensions were confined to the lymph node groups in thirty two and in twenty-one of these patients only to the same side of the diaphragm as the original lesions In one patient (Case 10) in whom the first extension was on the other side of the diaphragm this meant extension to an *adjacent* group The first extensions were localized outside the lymph node groups in seventeen patients in six of whom there was simultaneous extension within the lymph node groups Clinically then exclusively intranodular extension of the disease was initialy more common (32 patients) than extranodular (17 *patients*) The difference was significant at the 5 % level

The first extensions were noted within the first year after primary ...

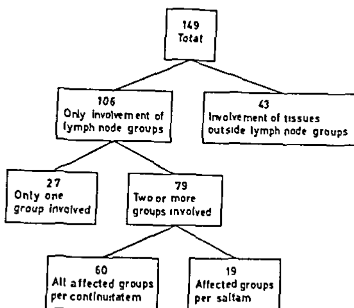


Fig 10 Patients grouped according to involvement before the beginning of treatment

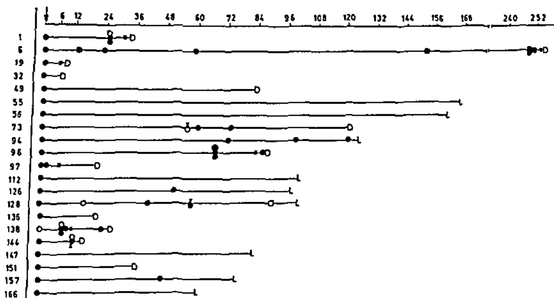


Fig 11 The further clinical course (months) in 21 patients in stage I extension to a lymph node group above the diaphragm (●) and below the diaphragm (○) recurrence within a lymph node group above the diaphragm (■) and below the diaphragm (□) first extension outside the lymph node groups (×) L=living D=dead

Table 4

Patients in sta e I and stage II grouped accordin to the histologic type of disease (according to LUKES *et coll 1966) and the further clinical course after the beginning of treatment*

	Histologic type				Total
	Lymphocyt ic predom inance	Nodular sclerosis	Mixed cellularity	Lymphocyt ic depletion	
No extensions noted	6	6	10		22
First exten ions only in the lymph node groups	8	10	12	2	32
First extensio s outside the lymph node groups	3	4	8	2	17
	17	20	30	4	71

mission of 99 months but who finally 256 months after the beginning of treat ment died from the disease A remission of at least 5 years after an extension was otherwise noted in only two patients (Cases 48 and 113) both of whom are still alive

Of the 71 patients in stages I and II 36 developed extensions outside the lymph node groups In three patients (Cases 128 139 and 158) extensions appeared outside the lymph node groups at 59 85 and 72 months respectively after the primary treatment and all three were still alive 44, 8 and 6 months later In the remaining thirty three patients the extensions outside the lymph node groups were diagnosed at a median of 31 (range 2 to 255) months from the beginning of treatment and these patients died at a median of 10 months later (range 1 to 66)

No correlation could be found between the length of the interval between the beginning of treatment and the time of the first extension outside the lymph node groups and the interval between the appearance of such extension and death

Thus in stages I and II the localization of the first extension seemed to be predictable to some degree and the disease tended to be confined to the lymph node groups for a comparatively long time

Clinical course in different histologic types The histologic types of each of the 71 patients in stages I and II are recorded in Figs 7 to 9 In about one third of the patients with lymphocytic predominance nodular sclerosis or mixed cel lularity no further manifestations were diagnosed clinically after the beginning of treatment (Table 4) while all the four patients with lymphocytic depletion

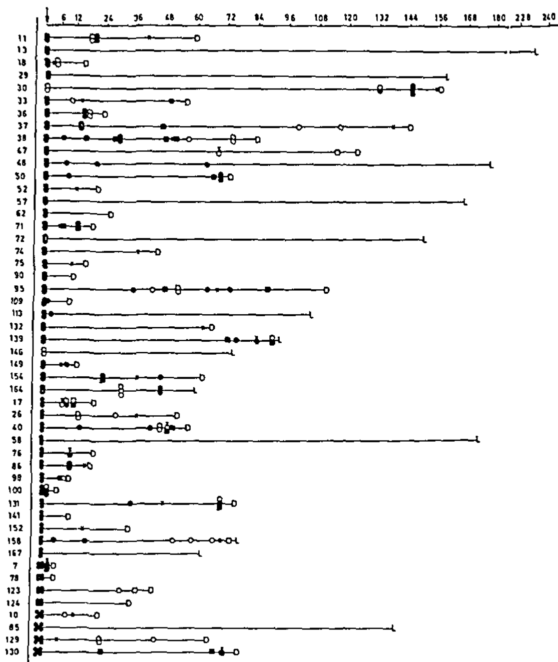


Fig 12 Further clinical course (months) in 50 patients in stage II (for interpretation of symbols see fig 11)

in 23 patients, in six not until 5 years or more had elapsed, and in one of these (Case 30) not until after a remission of 132 months from the beginning of treatment The longest course was noted in a patient (Case 6) who had several recurrences and extension to adjacent lymph node groups with the longest re

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developed further manifestations Among the 49 patients in whom further manifestations were diagnosed, the first extension appeared to be more often confined to the lymph node groups in the patients with lymphocytic predominance or nodular sclerosis than in those with mixed cellularity or lymphocytic depletion, but the difference was not statistically significant KELLER et coll (1968) found that 'noncontiguous dissemination, when it occurred, was more than twice as frequent in the mixed cellularity and lymphocyte depletion types compared to nodular sclerosis

SUMMARY

A retrospective study of 149 patients with Hodgkin s disease indicated that at the time of primary treatment the disease was generally confined to the main lymph node groups The progress of the condition from the first treatment is described in detail The investigation supports the concept that the initial spread of the disease is usually predictable

ZUSAMMENFASSUNG

Eine retrospektive Untersuchung von 149 Patienten mit Hodgkins Erkrankung zeigte dass bei Beginn der Strahlenbehandlung die Erkrankung sich auf die Hauptgruppen der Lymphdrusen begrenzte Die weitere Ausbreitung der Erkrankung nach dem Beginn der Behandlung wird im einzelnen beschrieben Die Analyse bestatigt die Annahme dass die ursprungliche Ausdehnung der Erkrankung richtig eingeschatzt werden kann

RÉSUMÉ

L étude retrospective de 149 malades atteints de maladie de Hodgkin a montré qu au moment du premier traitement la maladie était géneralement limitée aux principaux groupes de ganglions lymphatiques La progression de l affection a partir du premier traitement est decrite en détail Ce travail confirme l opinion que generalement l extension initiale de la maladie est prévisible

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RECURRENT CANCER OF THE CORPUS UTERI

Clinical significance of the relationship between survival and recurrence time

by

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Very little attention has been paid to the significance of recurrence in endometrial carcinoma Previous publications (RUBIN et coll 1963 BOUTSELIS et coll 1963 PRICE et coll 1965 SPEERT 1949 RUTLEDGE et coll 1958 FINN et coll 1950 BROWN et coll 1968 and DEDE et coll 1968) on recurrent cancer of the corpus have only touched upon this subject and have merely showed its relationship to survival No effort has been made to evaluate the clinical significance of time to recurrence i e what type of cases will have early recurrence and what type will have late recurrence and what kind of relationship exists between recurrence and survival times

It has been stated recently by KUROHARA et coll (1969) that the relationship between time to recurrence and survival time after recurrence is not always direct There are certain cases with indirect or no relationship between these time values

In this study the results of a detailed analysis of the relationship between time to recurrence after initial management the clinical and treatment factors and survival after recurrence are presented

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evaluated according to the recurrence time intervals defined above and according to combinations of short and long recurrence time and short and long survival time intervals. The point of demarcation of the latter interval was chosen near the median times Of the large numbers of tabulations obtained by computational analysis only a few of the essential ones have been included in this paper

Results

Table 1 represents the recurrence time periods in relation to the general clinical findings at the time of initial treatment of the cancer Eighty five per cent of the recurrences occurred during the early period and 15 per cent during the late period In general cases with initially high stage lesions and/or with large size uterus recurred earlier than those with low stage lesions and/or small size uterus Despite the limited data on uterine cavity depth measurements it is interesting to note that there was a tendency toward early recurrences in cases with cavities greater than 10 cm in depth

The initial treatment did not have any effect on recurrence time The relationships between survival time after recurrence and time to recurrence in the eight anatomical subgroups are shown in the diagrams of the accompanying figure

The relationships between the two recurrence time intervals and the type of initial treatment type of subsequent treatment for recurrences and survival rates at 2 and 5 years for the four subgroups of the anatomical patterns are given in Tables 2 and 3

Vaginal subgroup (UV LV UL LV) This includes recurrences of pure upper vagina lower vagina and upper and lower vagina These cases were combined in one group as the number of cases became small when the three vaginal subgroups were used 72 per cent of them occurring early and 28 per cent late On the whole the vaginal subgroup showed a direct relationship between survival time after recurrence and time to recurrence This relationship was true in cases with pure upper vaginal and pure lower vaginal lesions but it was significantly indirect in those few with upper and lower vaginal recurrences The proportion of cases treated initially with surgery alone and with intracavitary radium plus surgery in both periods was equal There was a higher proportion of cases treated subsequently for recurrences with radium and roentgen rays in the late period than in the early period

Pelvic subgroups (P(nf) P(f)) In this group 82 per cent of the recurrences were in the early period and 18 per cent in the late period There was a direct relationship between survival time after recurrence and time to recurrence for the non fixed pelvic subgroup but little or no relationship for the fixed pelvic sub

Table 1

Clinical variables in relation to time intervals of recurrence in carcinoma of the corpus uteri

Variables	Total	Early	Late
Number of cases	198	159	39
Mean age	60 7	61 9	59 6
Clinical stages	198		
Stage I	172	133	39
Stage II and higher	26	26	0
Uterine size	132		
Normal	72	48	24
>Normal	60	46	14
Uterine cavity size	58		
<10 cm	8	3	5
>10 cm	50	39	11
Type of treatment	198		
Radiation only	41	35	6
Subtotal hysterectomy	25	21	4
Subtotal hysterectomy and radium	10	7	3
Total hysterectomy	66	50	16
Total hysterectomy and radium	56	45	11

Method and Material During January 1, 1945 through December 1, 1964 there were 252 cases classified as having had recurrent adenocarcinoma or adeno-acanthoma of the corpus uteri One hundred ninety eight of these patients were dead by the time of writing and could be used for evaluation of survival and recurrence times However, since there were only 26 cases with stage II, or higher lesions, and only three cases with early cancer treated originally with radical hysterectomy these were excluded from the major portion of this study The remaining 169 cases (stage I dead) were evaluated in detail

Recurrence occurred according to the initial type of treatment as follows 63 cases after total abdominal hysterectomy, 48 cases after total abdominal hyster ectomy and radium, 25 cases after radium only, 23 cases after subtotal hyster ectomy and 10 cases after subtotal hysterectomy and radium

Recurrence time was divided into two periods short or early (6 months to 3 years), and long or late (more than 3 years) The same scheme of anatomical patterns as in a previous paper (KUROHARA et coll 1969) was employed, except that subgroups UV P, LV P, UV LV P were combined and denoted as pelvic (Pv), not fixed (nf) or fixed (f) to the lateral pelvic walls Computational analysis was carried out by methods previously described The distribution of the clinical and treatment variables among the anatomical subgroups of cases, were

Table 2

Relationships between recurrence time intervals and type of initial treatment type of subsequent treatment and survival in the vaginal and pelvic subgroups of stage I cases (minor types of surgical treatment such as laparotomy and tumor excision are not shown since they were small in number)

Total	Vagina (60 cases)		Pelvic (42 cases)	
	Early	Late	Early	Late
Total	43	17	34	8
Initial treatment				
Surgery	29	11	20	5
Radium	0	1	2	1
Surgery and radium	14	5	12	2
Subsequent treatment	9			
Roentgen rays	9	1	19	4
Radium	21	8	6	1
Roentgen and radium	13	8	9	3
Survival				
2 years	10/43	13/17	8/34	6/8
5 years	7/43	8/17	1/34	1/8

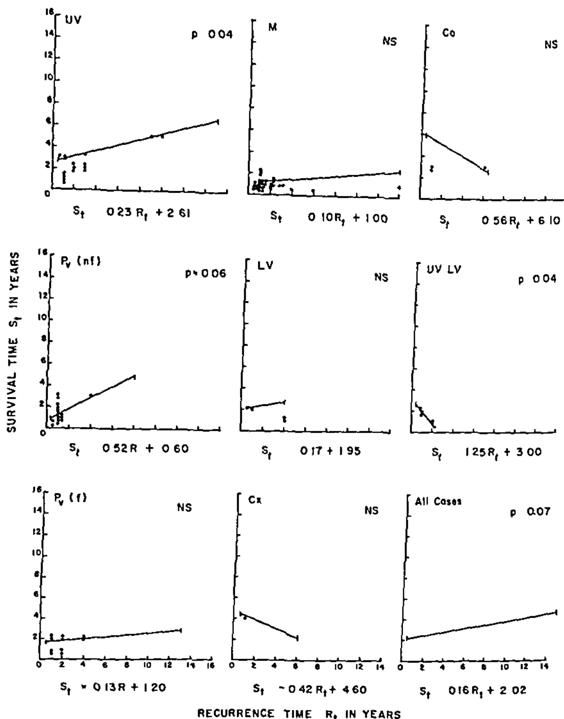
group Equal proportions of cases in both periods were treated with surgery alone radium or radium and surgery Subsequent treatment for recurrences did not seem to influence the outcome

Metastatic subgroup (M) In this group 80 per cent of the recurrences occurred in the early period and 20 per cent in the late period A higher proportion of cases were treated only with radium in the early period than in the late period (5/31 versus 0/8) By including the cases treated with intracavitary radium and surgery the proportion of cases in both periods became nearly equal Survival was essentially poor and there was essentially no relationship between survival after recurrence and time to recurrence Subsequent treatment was mainly palliative varying from roentgen irradiation to hormonal therapy

Uterine subgroup (Co Cx) Here 80 per cent of the recurrences were in the early period and 20 per cent in the late period The relationship between survival after recurrence and time to recurrence was indirect for both the corporeal and

lesions They are arranged in decreasing order of their regression coefficients The statistics for all cases are also shown

Significance levels obtained by the Spearman's rank method for the UV Pv (nf) and all cases subgroups were 0 03 0 06 and 0 04 respectively those for the others with ten or more cases were not significant.



The relationships between time to recurrence and survival time after recurrence are shown according to the anatomical patterns of recurrences in stage I adenocarcinoma of the corpus uteri The scattergrams estimated linear regression lines regression equation and significance level for the null hypothesis that the population coefficient is equal to zero are shown for the upper vaginal (UV) non fixed pelvic (Pv (nf)) fixed pelvic (Pv (f)) metastatic (M) lower vaginal (LV) cervical (Cx) corporeal (Co) and upper and lower vaginal (UV LV)

to recurrence time intervals types of treatment and certain other variables, the number of cases in each of the subgroups became too small to be able to offer any conclusions Furthermore in the final analysis the few initially advanced cases were excluded in order to make the series more homogenous with respect to stage and to remove complicating factors peculiar to them but not to early lesions

Generally we found that cases with advanced clinical stage with or without large size uterus have earlier recurrences No differentiation between adenocarcinoma and adenoacanthoma cases was attempted They were shown to behave similarly (KUROHARA et coll 1969) Other factors such as age and type of treatment did not have any influence on the time to recurrence

Looking at the effect of initial treatment in relation to the different anatomical sites of recurrence we found that the type of treatment failed to have any influence on the recurrence time within the vaginal pelvic and metastatic categories In the uterine subgroup surgery was associated with early recurrences (8 22 versus 1/6) This occurred in cases with cervical recurrences following subtotal hysterectomy performed elsewhere

The relationship between survival time after recurrence and time to recurrence is in general direct However, this relationship depends to a large extent on the anatomical patterns of recurrence The formation of the latter in turn depends on the method of initial treatment employed as has been shown by KUROHARA et coll

Vaginal recurrences and pelvic recurrences showed a direct relationship The best salvage was obtained in the late vaginal recurrences Probably the combination of roentgen irradiation and radium which was utilized more often in the late recurrent cases than in the early ones may partially explain these better results Subsequent treatment in the pelvic subgroup did not have any effect

The metastatic subgroup showed only a slightly direct or no relationship between these time values Survival was poor and type of subsequent treatment had no effect on the outcome

The uterine subgroup cases showed an indirect relationship in these time values This was influenced by the anatomical pattern the initial treatment and the subsequent treatment The results appeared to be better if we detected these cases early and treated the corporeal recurrences with hysterectomy with or without intracavitary radium and the cervical ones with vaginal radium and cervicectomy

SUMMARY

Recurrence and survival times in 198 cases of adenocarcinoma of the corpus uteri have been analyzed Survival time after recurrence and time to recurrence after initial treatment

Table 3

Relationships between recurrence time intervals type of initial treatment type of subsequent treatment and survival in the metastatic and uterine subgroups of stage I cases

	Metastatic (39 cases)		Uterus (28 cases)	
	Early	Late	Early	Late
Total	31	8	22	6
Initial treatment				
Surgery	10	3	8	1
Radium	5	0	13	4
Surgery and radium	16	5	1	1
Subsequent treatment				
Roentgen rays	18°	1°	2*	1*
Radium	1	1	12	3
Roentgen rays and radium	2	0	2	1
Survival				
2 years	3/31	2/8	12/22	3/6
5 years	0/31	1/8	8/22	1/6

° Cases not shown in the table were treated with hormones and/or chemotherapy

* Cases not shown in the table were treated with total hysterectomy for their recurrences Minor types of surgical treatment such as laparotomy and tumor excision are not shown as they were very small in number

cervical cases There was a higher proportion of cases in the early period treated with surgery alone Most of these cases were cervical recurrences after subtotal hysterectomy only performed elsewhere The best survival after recurrence was obtained when the lesions were discovered early and treated with total abdominal hysterectomy *with or without intracavitary radium in the corporeal recurrent* cases (10/16 versus 1/4) and cervicectomy or with radium in cervical ones (2/6 versus 0/2)

Discussion

The factors that influence the relationship between survival time after recurrences and time to their detection after initial treatment of cases with adenocarcinoma of the corpus uteri are numerous Most of them are unknown to us

In this study, although we started with a fairly large number of cases, we were obliged to consider only four anatomical categories (stages) of recurrent adenocarcinoma The reason for this is that when the series was segregated according

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SELECTIVE UPTAKE OF A RADIOACTIVE DRUG INTO HUMAN TUMOUR CELLS GROWING IN TISSUE CULTURE

by

P P DENDY

The possible treatment of patients with cancer of all types by means of radioactive drugs has been actively investigated for a number of years (see for example MITCHELL 1960 1967 MITCHELL KING MARRIAN & CHIPPERFIELD 1963) It is a method of great potential value which depends on two fundamental requirements The first is the selection of an organic compound which is reasonably stable and which shows a high degree of selective absorption into tumour cells relative to normal cells In comparative studies of normal and tumour cells very few differences which can be exploited in this way have been found and the selection of a paraquinone type compound in Cambridge was made many years ago as a result of extensive screening work in tissue culture (MITCHELL & SIMON REISS 1952) The second requirement is that the compound selected can be labelled with a firmly bound radioisotope at a sufficiently high specific activity to produce therapeutic irradiation in situ The most suitable radioisotope to incorporate for this purpose is tritium since the soft β particles emitted by tritium decay have a maximum range of about 6μ in tissue of unit density and the biological effects are accordingly strictly localised

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may have direct, indirect or no relationship depending on the anatomical site of recurrence The type of *subsequent treatment* has *a greater effect* than that of the initial treatment in changing this relationship within the cervical corporeal, or upper vaginal subgroups but they have no effect within subgroups of cases with pelvic or distant recurrences

ZUSAMMENFASSUNG

Die Zeitintervalle fur Wiederauftreten und Überleben bei 198 Fallen von Adenocarcinomen des Corpus uteri wurden analysiert Die Überlebenszeit nach dem Wiederauftreten und die Zeit des Wiederauftretens nach der Initialbehandlung konnen in Abhangigkeit vom anatomischen Sitz des Wiederauftretens einen direkten indirekten oder keinen Zusammenhang haben Die Art der nachfolgenden Behandlung hat eine grossere Bedeutung fur die Anderung dieser Beziehung innerhalb der cervicalen corporalen oder oberen vaginalen Untergruppen als die Initialbehandlung sie hat jedoch keine Bedeutung innerhalb der Untergruppen von Fallen mit Becken oder entfernten Metastasen

RÉSUMÉ

Les auteurs analysent le delai de récidive et le temps de survie de 198 cas d adénocarcinome du corps de l utérus La durée de survie après la récidive et le délai entre le premier traitement et la récidive sont en rapport direct ou indirect ou sans rapport entre eux suivant la localisation anatomique de la récidive Le type du deuxieme traitement a plus d influence que celui du traitement initial pour modifier ce rapport dans les groupes de récidives cervicales corporéales ou vaginales supérieures mais il n a pas d effet dans les groupes de récidive pelvienne ou a distance

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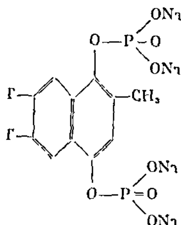
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The drug used in these studies is 2 methyl 6 7 ditritio 1 4 naphthaquinol bis (disodium phosphate)



TRK 219

This is now prepared by the Radiochemical Centre, Amersham, and will be designated TRK 219, following the catalogue of the Radiochemical Centre A modified tritiation procedure, suggested by Dr D H MARRIAN of this department has enabled the preparation of batches of material for which the specific activity frequently does not differ significantly from the theoretical maximum of 58 2 Ci/millimole Good results have been obtained with this compound during the past three years but inconsistencies have sometimes been noted both in tissue culture and clinically

These experiments were therefore designated to work out more fully the differences in response of cultured tumour cell lines and freshly cultured normal cell strains to TRK 219 The methods adopted are similar to those developed in this laboratory by SIMON REUSS (1961)

Experimental Numerous cell types have been used and they are listed below together with details of the culture media in which they were grown

A HEp/2 cells obtained from the Wellcome Research Laboratories and cultured in 90 parts Eagles medium + 10 parts foetal calf serum (Flow Laboratories) + 1 part $NaHCO_3$ solⁿ at 56 mgm/ml

B HeLa cells cultured in the laboratory for many years and grown in 90 parts Eagles medium + 10 parts foetal calf serum (Flow Laboratories) + 1 part $NaHCO_3$ sol at 56 mgm/ml

C Fresh monkey kidney cells (M K) growing in 100 parts 199 medium + 2 5 parts Gibco foetal calf serum

D Fresh human amnion cells (H A) growing in 80 parts Eagles medium + 20 parts human serum + 1 part $NaHCO_3$ solⁿ at 56 mgm/ml

E Fresh human embryonic skin fibroblast cells (H E S) cultured in 199 medium + 2 5 parts Gibco foetal calf serum

F Fresh human embryonic lung cells cultured in 80 parts Eagles medium + 20 parts

foetal calf serum (Gibco)+5 parts of 5% lactalbumin hydrolysate+1 part of $NaHCO_3$ sol at 50 mgm/ml

To set up an experiment 4 ml of culture medium containing approximately 2.5×10^4 cells/ml were placed in a 5 cm diameter petri dish which contained 4 mm×12 mm cover slips. Two days later when the cells were usually growing well they were washed twice in saline at pH=7.2 immediately prior to use

The radioactive drug was stored in the vapour above liquid nitrogen from the time of arrival until 24 hours before use It was allowed to come up to −80 C overnight and thawed out rapidly immediately prior to use For most of the experiments the radioactive material was diluted to the required molarity in physiologic saline at pH=7.2 and 2 ml of this solution was placed in each petri dish for 10 minutes Variations on this procedure designed to test certain points were (1) dilution of the drug in serum free culture medium (2) exposure of the cells to the drug for time intervals varying from 3 to 60 min (3) adjustment of the pH of the saline solution to other than 7.2 and (4) the addition of ordinary Synkavit (Roche Products Ltd) to reduce the specific activity when working at molarities greater than 1.5×10^{-4} M

After exposure to the drug the coverslips were immediately rinsed three times in saline and fixed in methanol for 5 minutes To reduce the label adhering to the glass surface without reducing that associated with the cells the coverslips were allowed to stand for 15 minutes in distilled water Autoradiograms were then prepared in the usual manner using Ilford K2 liquid emulsion Those which were to be developed less than three hours later were dried rapidly using a hair drier All the other slides were allowed to dry normally a process which occupied not longer than 30 minutes and then exposed for at least 16 hours

After exposure times which varied from 25 minutes to 3 months the autoradiograms were developed in Kodak D19b for 5 minutes fixed in 10% Johnsons Fixol to clear and stained with Ehrlich Haematoxylin Except for one experiment performed at the lowest molarity a suitable method was used to ensure that no appreciable latent image fading had occurred (BASERGA 1967) Slides which received different exposures could thus be compared Cells in all stages of the mitotic cycle were labelled fairly uniformly and therefore grain counts were made over the nuclear region of well spread-out cells Counts were generally made over 50 nuclei on each of two coverslips averaged and expressed as grain count per nucleus per hour exposure to the autoradiographic emulsion Finally the counts were normalised to a standard specific activity of 58.2 curies/millimole the theoretical maximum for TRK 219 By making strictly comparative studies and following this procedure the numerous problems involved in quantitative autoradiography with tritium isotopes (see for example ROGERS 1967) were avoided

Results

Major experiment In the routine test carried out on each batch of material prior to clinical use, TRK 219 is diluted to circa 1.6×10^{-4} M in physiologic saline and used according to the procedure outlined above All autoradiograms are exposed for 16 hours, and Fig 1 shows the results for a batch which was suitable for clinical use Fig 2 shows the results for the only batch out of the last eleven which was not satisfactory and had to be discarded

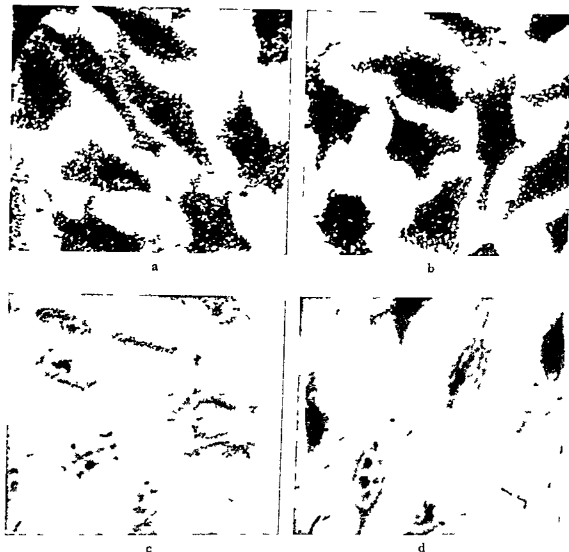


Fig 1 Autoradiograms of material batch 109 TRK 219 acceptable for clinical use labelled as follows a) HEP/2 cells b) HELA cells c) MK cells d) HA cells

counts to be made and therefore duplicate slides were developed after half an hour, again following the procedures outlined above Results have been averaged over 10 batches of TRK 219 and are shown in Table 1

The errors quoted there, and those shown in Fig 3, are the standard errors for a single batch of TRK 219 relative to the mean value for a number of different batches The standard error of the mean is of course lower by a factor equal to the square root of the number of batches tested Thus there was on average 30 times more TRK 219 taken up into tumour cells than into M K cells and for some batches the figure was as high as 100 times

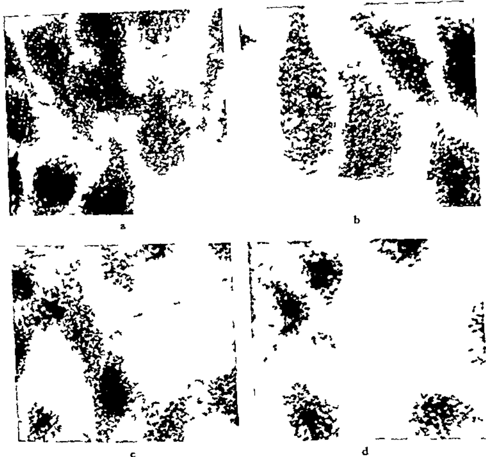


Fig 2 Autoradiograms of material batch 110 TRK 219 unsatisfactory for clinical use labelled as follows a) HEP/2 cells b) HELA cells c) MK cells d) HA cells

A more detailed plot of the results for all cell types at different molarities is shown in Fig 3 Where a group of results for the same cell type fell close together the results were averaged and errors are shown Features of these results are as follows

1 On a log log scale there is a linear increase in uptake of label with increasing molarity for M K cells and the slope of the line is approximately 1 This would be expected on the simplest kinetic model in which uptake is proportional to the external concentration

2 The uptake into normal freshly cultured human cell strains is generally lower than that into M K cells

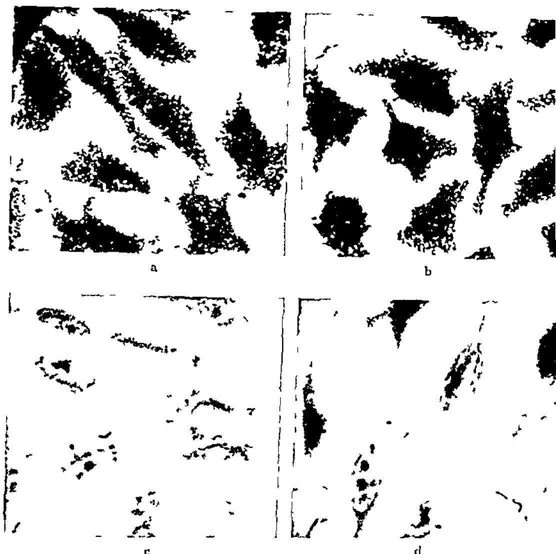


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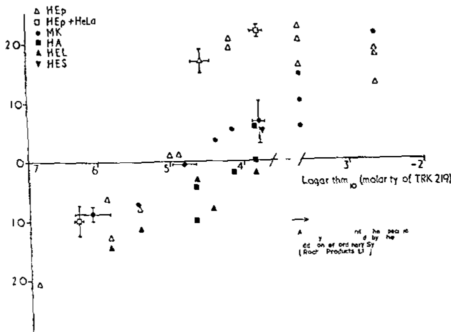


Fig 3 The uptake of TRK 219 plotted on a log log scale against the molarity of the administered material for a number of cell types

A paired sample t test shows that the increase in label between 3 and 10 min is significant at the 1 % level and it is reasonable to conclude that metabolic uptake is being observed

In some experiments the uptake of TRK 219 diluted in serum free medium was compared with that of TRK 219 diluted in physiologic saline The results showed that for labelling times as short as 10 min followed by immediate fixation the carrier medium is relatively unimportant and at 1.7×10^{-4} M selective uptake into tumour cells was again observed

In other experiments the pH of the physiologic saline was altered in the range 6 0 to 8 2 Results showed that the uptake of label into tumour cells was fairly constant in the pH range 7 2—8 4 but fell at more acid pH reaching a low level in the region of pH = 6 0

Discussion

In these experiments the uptake of TRK 219 into the cells in established lines derived from human tumours has been compared with its uptake into freshly

Table 1

Results showing the selective uptake into tumour cells when TRK 219 at circa $1\ 7 \times 10^{-4}$ M was administered

Molarity of TRK 219	Cell type	Rate of uptake of label grains/nucleus/hr	Number of batches
$(1\ 7 \pm 0\ 2) \times 10^{-4}$	HEp/2	145 ± 33	10
$(1\ 6 \pm 0\ 1) \times 10^{-4}$	HeLa	132 ± 27	5
$(1\ 7 \pm 0\ 2) \times 10^{-4}$	M K	$4\ 8 \pm 4\ 0$	10

Table 2

The dependence of uptake into HEp/2 cells on time of exposure to the drug

TRK 219 batch number	119	120	120	121
Label after 3 minutes grains/nucleus/hr A R G	43	71	34	61
Label after 10 minutes grains/nucleus/hr A R G	154	167	192	136

3 At low molarities the results for tumour cells agree closely with those for normal cells Just above 10^{-5} M there is a dramatic increase in uptake into tumour cells and in the region from $1\ 5 \times 10^{-5}$ M to $1\ 5 \times 10^{-4}$ M the selective uptake already recorded in the routine test is observed

4 Above $1\ 5 \times 10^{-4}$ M, the autoradiographic technique can only be used if the specific activity of the TRK 219 is reduced Errors of dilution are introduced and the assumption that the added molecules are biologically indistinguishable from the hot molecules is not necessarily justified in this instance Results indicate that this may be another region in which the rate of uptake of TRK 219 into tumour cells established in tissue culture changes rapidly for small changes in molarity In particular it would appear that as the molarity is increased above 2×10^{-4} M, the enhanced uptake into tumour cells is quickly lost

Subsidiary experiments The possibility that the increased label observed over the tumour cells within a limited range of molarities might be due simply to physical adsorption on the cell surface, without metabolic uptake, had to be examined To do this two HEp/2 cell coverslips were removed from the TRK 219 in several experiments at only 3 min, rinsed in saline, and fixed The results for these cultures are compared with those for normal ten minute labelled cultures in Table 2

that much of the label noted in normal cells may result from impurities and the presence of even 1—2 % of the latter can seriously influence the apparent specificity of TRK 219 for tumour cells

The results can be used to estimate the radiation dose to a cell Exposure to 1.5×10^{-4} M TRK 219 at 58 curies millimole for 10 min produces in the subsequent autoradiogram circa 150 grains over each nucleus per hour Assuming an autoradiographic efficiency of 3 % for monolayer cells in tissue culture (CLEAVER 1967) this corresponds to 5 000 disintegrations per hour or a dose rate to the nucleus of the order of 5 000 rad per hour (GOODHEART 1961) Thus the incorporated TRK 219 produces an internal source of radiation which from estimates based on modern survival curve theory (ELKIND & WHITMORE 1967) would allow a practically negligible probability of survival

In conclusion one must ask to what extent these results suggest that the elegant therapeutic treatment outlined in the introduction is available clinically On the one hand they show that a reasonably stable tritiated compound which is incorporated selectively into tumour cells in tissue culture is available and further that the amount of tritium incorporated in this way is more than sufficient to cause lethal damage to the cells On the other hand several important problems still remain Will all tumour cells in vivo show the same selective uptake that HeLa and HEp cells show in vitro or will some preliminary screening of biopsy material from individual patients prove advantageous by selecting patients whose tumour cells show selective uptake? Is it possible to introduce the radioactive material to the site of the tumour at the required pH and at a concentration which falls within fairly narrow limits? Is the TRK 219 sufficiently stable to be incorporated without appreciable breakdown to materials which are probably actively taken up by normal cells?

All these problems lie beyond the limitations of experiments in tissue culture but much of the work of MITCHELL (1965 1967) and co-workers both with animals and with patients indicates that further intensive studies are desirable

Acknowledgements

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SUMMARY

The uptake of 2 methyl 6 7 ditritio-1 4 naphthaquinol bis (disodium phosphate) into several cell types growing in tissue culture has been studied autoradiographically Results show that provided the drug is administered at a molarity between 1.5×10^- [illegible] M and 1.5×10^{-4} M the uptake into human tumour cells established in tissue culture can be as much as 100 times greater than that into freshly cultured normal cells Outside this narrow range of molarities the enhancement is rapidly lost

cultured normal cells from human and other mammalian tissues It is perhaps worthwhile to repeat the salient features of the experimental details

1 A cell density was chosen so that the cells would be nearly confluent at 48 hours

2 Cultures were washed twice in saline at pH = 7 2 before use

3 TRK 219, which had been stored carefully to prevent decomposition was allowed to come into contact with the cells for 10 minutes

4 The system could be expected to be well oxygenated during this short time

Under these conditions the uptake of TRK 219 into tumour cells was on average 30 times higher than that into M K cells provided that the molarity of the drug was between $1\ 5\times10^{-5}$ M and $1\ 5\times10^{-4}$ M The average enhancement relative to normal human tissues was somewhat higher at these molarities but outside this limited range the enhancement was rapidly lost We can offer no explanation at present for the loss of selective uptake outside this limited range of molarities but the observation by MARRIAN (personal communication) that in vitro incubation of cultured HeLa cells in solutions of TRK 219 at 37°C leads to rapid breakdown of the TRK 219 may be relevant The process involves dephosphorylation and among the products are menadiol 1 phosphate, thiodione and menadione, the latter of which may be the compound actually incorporated by the tumour cells No breakdown products could be detected when embryonic mouse fibroblast cells were incubated with TRK 219 for comparable lengths of time The idea that metabolic processes may occur prior to incorporation of the label is supported by qualitative observations in the present studies that the uptake was nearly always lower in any region where a coverslip was rather sparsely populated with cells

The observations recorded in Table 2 show that true metabolic uptake into the tumour cells was being recorded and subsidiary experiments showed that the elevated uptake into tumour cells is relatively independent of pH provided the latter can be maintained above circa 7 0

In these results, one aspect which has yet to be investigated in detail concerns the purity of the administered material Reference to Table 1 shows that (for different batches of TRK 219) the variation in labelling over M K cells expressed on a percentage basis is much larger than that over tumour cells Furthermore, the deterioration of relative uptake of label as a result of storage, or repeated thawing and re freezing of the same TRK 219 solution is caused not by any appreciable decrease in the label over tumour cells but by a marked increase in the label over M K cells For example, the radiochemical purity of one batch of material fell from 96 % upon arrival to 80 % after a certain amount of thawing and re freezing over a period of 6 weeks The label over HEp cells did not fall significantly but that over M K cells rose by a factor of 5 This suggests

FROM THE RADIOISOTOPE AND METABOLIC UNITS, ST VINCENT S HOSPITAL AND THE DEPARTMENT OF MEDICINE UNIVERSITY COLLEGE, DUBLIN IRELAND

CHROMIUM 51- EDTA IN THE DETERMINATION OF GLOMERULAR FILTRATION RATE

by

T G BRIEN, R O HAGAN and F P MULDOWNEY

The glomerular filtration rate (GFR) is a measurement of considerable importance in the assessment of renal function It is commonly determined from the 24 hour hour endogenous creatinine clearance although it is recognised that this method is prone to error because creatinine may be secreted by the renal tubules Thus creatinine clearance may grossly overestimate the true glomerular filtration rate particularly in the nephrotic syndrome (BERLYNE et coll 1964) Nevertheless the use of the endogenous creatinine clearance as a measurement of the glomerular filtration rate remains a most useful tool in the diagnosis of renal disorders

Radioactive chromium complexed with ethylene diamine tetracetic acid (^{51}Cr EDTA) appears to fulfil the requirements for an ideal clearance sub tance (Editorial in Lancet 1965) and has been shown to be excreted similarly to inulin when given by the continuous infusion technique (GARNETT, PARSONS & VEALL 1967) even when the creatinine clearance was markedly elevated compared to the inulin clearance (FAVRE & WING 1968) As inulin is generally recognised as the standard substance for measuring the glomerular filtration rate any substance

Submitted for publication 18 October 1968

ZUSAMMENFASSUNG

Die Aufnahme von 2 Methyl 6 7 ditritio 1 4 Naphthaquinol *bis (Dinatriumphosphat)* von verschiedenen in Gewebekulturen wachsenden Zellarten wurde histologisch mit Autoradiographie studiert Wenn die Substanz in einer Konzentration zwischen $1{\cdot}5 \times 10^{-5}$ M und $1{\cdot}5 \times 10^{-4}$ M gegeben wurde zeigte es sich dass die Absorption bei menschlichen Tumor zellen in Gewebekulturen fast hundertmal grosser sein kann als die Absorption in neu kul tivierten Normalzellen Ausserhalb diesem engen Bereich der Konzentration geht diese Steigerung schnell verloren

RÉSUMÉ

L auteur a étudié par autoradiographie la fixation du 2 méthyl 6 7 ditritio 1 4 naph thaquinol bis (disodium phosphate) dans plusieurs types de cellules maintenues en culture de tissus Les résultats montrent que si la drogue est administree à une molarité entre $1{\cdot}5 \times 10^{-5}$ M et $1{\cdot}5 \times 10^{-4}$ M la fixation dans les cellules tumorales humaines entretenues en culture de tissus depuis plusieures annees peut etre 100 fois plus élevée que la fixation dans les cellules normales en culture récente En dehors de cet étroit écart de molarité cette augmentation de la fixation est rapidement supprimée

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separated These times need not be adhered to rigorously provided the exact time of sampling is noted Where possible the urine excreted between the 120 min and 240 min samples was collected and the volume recorded Four millilitre aliquots of plasma urine and standard were counted, in a well type scintillation counter and corrected for background

When counts versus time is plotted on semi log paper two exponential curves can be resolved an early mixing phase between plasma and interstitial fluid (the fast curve) and a later decay due to renal excretion (the slow curve) (Fig 1)

The glomerular filtration rate was calculated from the following equation (SAPIRSTEIN et coll 1965)

$$GFR = \frac{I\lambda_1\lambda_2}{A\lambda_2 + B\lambda_1} \qquad (1)$$

where I = total counts in the dose λ_1 and λ_2 are the slopes of the fast and slow curves respectively and A and B are the respective intercepts of the fast and slow curves

An alternative calculation using the urine collection is based on the method of BIANCHI & TONI (1964)

$$GFR = \frac{X_e}{\int_{t_1}^{t_2} Xp\,(t)\,dt} \qquad (2)$$

where X is the amount of substance eliminated between t_1 and t_2 and $Xp\ (t)$ is a function describing the change in plasma concentration with time

Since the curve has become monoexponential by two hours $Xp(t) = X_{120}\,e^{-\lambda t}$ where is the slope of the line and X_{120} is the plasma concentration at 120 minutes The integral then simply reduces to

$$\frac{X_{120}}{\lambda}\left[e^{-\lambda t_1} - e^{-\lambda t_2}\right] \qquad (3)$$

where t_1 and t_2 are 120 and 240 minutes respectively For ease of calculation it should be noted that the constant λ is identical with λ_2 of eq (1)

As these methods of calculation proved somewhat time consuming a computer programme was written in Fortran II for use on an IBM 1620 computer (copies are obtainable from the author on request) This programme accepts the raw data from the scintillation counter and computes the glomerular filtration rate by both methods

Twenty four hour creatinine clearances were performed in the Metabolic Laboratory St Vincent s Hospital The eight cases now reported were unselected

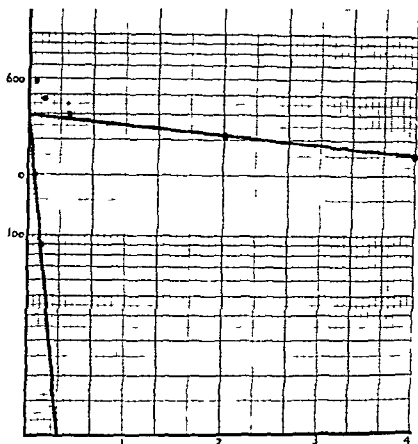


Fig 1 Semi log plot of plasma radioactivity (ordinate in counts per minute) against time (abscissa hours) The curve is resolvable into two single exponential components

which gives similar results to inulin over a wide range of values and in all conditions, but without the difficulty of chemical estimations of inulin, seems worthy of investigation

In this paper we describe a method of determining the filtration rate using a single injection of ^{51}Cr EDTA, which we believe is suitable for routine hospital ward use, it is not necessary to set up an infusion or to collect urine specimens

Material and Methods The ^{51}Cr EDTA was obtained from the Radiochemical Centre Amersham, England, and diluted with isotonic saline to give a concentration of 3 5 μCi/ml Ten millilitres of this solution was administered intravenously to the patient from a pre calibrated syringe, while 1 ml was diluted with water to 100 ml to serve as a standard At 5, 10 15 120 and 240 minutes after injection, 10 ml of blood was taken, placed in heparinized tubes, and the plasma

Discussion

Previous authors (GARNETT et coll 1967, FAVRE & WING 1968) have shown that the ^{51}Cr EDTA clearance corresponds very closely with the inulin clearance when estimated by the standard infusion technique quoting r values of 0 995 and 0.992 respectively The renal handling of ^{51}Cr EDTA and inulin would therefore appear to be identical Since ^{51}Cr EDTA is not bound by plasma proteins and is not taken up by any organ in the body it does not suffer from the disadvantages of radioactive vitamin B_{12} which for a while had achieved some popularity as an agent for the estimation of the glomerular filtration rate (WEEKE 1968)

The method is not affected by proteinuria or extraneous chromogens in plasma or urine and is particularly useful in cases where urine collection is difficult or impossible e g in incontinent patients We have used the method successfully to measure glomerular filtration rate in cases of ureterosigmoidostomy and colostomy with concomitant renal disease in whom the collection of urine was impossible Due to its lack of beta emission the radiation hazard is small The calculated radiation dose to the kidneys from 35 μCi dose is only 5 mrad, of the same order as the natural background radiation in a week

GARNETT et coll (1967) have also reported a series of 32 cases in which the ^{51}Cr EDTA clearance was measured after single injection and the results compared with the 24 hour endogenous creatinine clearance They again report a high degree of correlation ($r = 0\,948$) but emphasize that the method cannot be used in cases of oedema since equilibration of the complex may take up to 12 hours in such instances.

There is no readily apparent explanation for the increased slope of the line relating the 2 hour urinary excretion method with the plasma disappearance method shown in Fig 3 Incomplete emptying of the bladder at 2 hours after the injection could account for an increase in the amount excreted between 2 and 4 hours but while this may have occurred in some instances it could hardly account for the regularity of the increase observed

In practical terms the greatest source of error in the determination the glomerular filtration rate from the creatinine clearance is incomplete or inaccurate collection of urine Failure to provide a complete 24 hour collection particularly when the urine volume is low would give rise to far greater errors than any arising in the laboratory While it is not suggested that the method reported here is likely to supplant the 24 hour creatinine clearance it could provide a useful check on the accuracy of creatinine clearances which are clinically doubtful or be used to determine the glomerular filtration rate when the creatinine clearance is difficult or impossible

The possibility also exists that by monitoring the externally detectable radiation

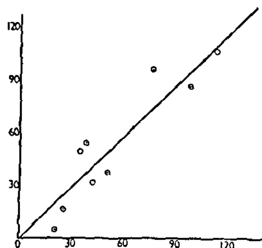


Fig 2 ^{51}Cr EDTA clearance (plasma method) (abscissa) versus 24 hour endogenous creatinine clearance (ordinate) $y = 0\ 98x - 1\ 0$ $r = 0\ 91$

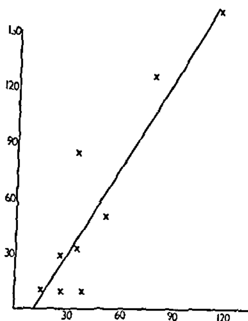


Fig 3 ^{51}Cr EDTA clearance (plasma method) (abscissa) versus urine method (ordinate) $y = 1\ 65x - 17\ 6$ $r = 0\ 91$

and generally referred to the Radioisotope Department for confirmation of an abnormal creatinine clearance or because the creatinine clearance gave an unexpected result

The results obtained using the plasma disappearance curve against 24 hour endogenous creatine clearances performed about the same time are plotted in Fig 2

The correlation between the two methods was $r = 0\ 914$ and the equation of the regression line $y = 0\ 984x - 1\ 03$, where y is the creatinine clearance and x the ^{51}Cr EDTA clearance This relationship is as good as that found between inulin clearance and creatinine clearance by FAVRE & WING ($r = 0\ 908$, $y = 1\ 28x - 2\ 49$) who found a very close relationship between inulin clearance and ^{51}Cr EDTA clearance ($r = 0\ 992$, $y = 1\ 02x - 0\ 95$)

A plot of the ^{51}Cr EDTA clearance measured by both the plasma disappearance curve and the 2 hour urinary excretion method in nine subjects is presented in Fig 3 The correlation coefficient between the two methods is again high ($r = 0\ 91$) but the regression equation $y = 1\ 649x - 17\ 63$ shows that the urinary excretion method gives a higher estimate of the clearance over most of the physiologic range

RÉSUMÉ

Description d'une méthode de détermination du taux de filtration glomerulaire d'après les modifications de la concentration plasmatique apres une seule injection de ^{51}Cr EDTA Les auteurs présentent les resultats obtenus chez neuf malades et les comparent avec la clearance a la creatinine endogene en 24 heures Ils ont obtenu de hauts degres de correlation

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SAPIRSTEIN L A VIDT D G MANDEL M J and HANUSEK F Volumes of distribution and clearances of intravenously injected creatinine in the dog Amer J Physiol 181 (1955) 330

WEEKE E ^{57}Co-cyanocobalamin in the determination of the glomerular filtration rate Scand J clin Lab Invest 21 (1968) 139

over the heart the shape of the plasma disappearance curve shown in Fig. 1 could be determined. A single blood sample would then suffice to determine the exact position of the curve since the count rate over the heart would bear a constant relationship to the plasma concentration of the isotope.

It is also possible that ^{51}Cr EDTA may prove to be a useful substance for renography. Radioiodinated dyes and contrast media may contain a proportion of free iodide or be degraded in the circulation to release iodide which is subsequently taken up by the thyroid. ^{51}Cr EDTA would appear to be free from any such disadvantages.

Addendum in proofs

At the expense of some decrease in accuracy the plasma curve method can be simplified by neglecting the initial fast phase and assuming that mixing takes place instantaneously. Eq. (1) then reduces to

$$GFR=\frac{I}{B} \tag{4}$$

using the same notation as before. Only two blood samples are now required, namely those at 120 and 240 minutes. Comparison of twenty clearances calculated by both methods gave a correlation of 0.99 and a regression equation $y=0.82x+6$ where y is the clearance as calculated from eq. (1) and x is the clearance as calculated from eq. (4).

Acknowledgements

We wish to acknowledge the assistance of Miss M. Swan of the Metabolic Unit, St. Vincent's Hospital, who carried out the creatinine clearances, and of Mrs P. Moriarty of the Computer Centre, University College Dublin, who assisted with the computer programme.

SUMMARY

A method of determining the glomerular filtration rate from the change in plasma concentration of a single injection of ^{51}Cr EDTA is described. Results in nine cases are presented and compared with the 24 hour endogenous creatinine clearance. A high degree of correlation was obtained.

ZUSAMMENFASSUNG

Eine Methode, um die Geschwindigkeit der Glomerulusfiltration aus der Änderung der Plasmakonzentration nach einer einfachen Injektion von ^{51}Cr EDTA zu bestimmen, wird beschrieben. Die Ergebnisse in 9 Fällen werden dargestellt und mit der 24 Stunden endogenen Kreatinin-Clearance verglichen. Eine hochgradige Korrelation wurde erhalten.

RÉSUMÉ

Description d une méthode de determination du taux de filtration glomerulaire d apres les modifications de la concentration plasmatique apres une seule injection de ^{51}Cr EDTA Les auteurs présentent les resultats obtenus chez neuf malades et les comparent avec la clearance a la créatinine endogène en 24 heures Ils ont obtenu de hauts degrés de cor rélation

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FROM THE DEPARTMENTS OF MEDICINE, RADIOTHERAPY AND DIAGNOSTIC CYTOLOGY,
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TUMOUR CELLS IN PERITONEAL RINSING FLUID

by

B LINDQVIST, G MICHAELSON, N E SATERBORG and T ÅNGSTROM

Cytologic examination can establish a correct diagnosis in 80 to 90 per cent of cases of ascites as a result of malignant tumour (VON HAAM 1962), although few laboratories attain this level Carcinoma of the pelvic organs in cases without ascites has been diagnosed by transvaginal injection of fluid into the pouch of Douglas, with subsequent aspiration and cytologic examination of the fluid (GRAHAM et coll 1964, LOWHAGEN et coll 1967) Peritoneal carcinosis in cases of malignant tumours of the abdomen without ascites can usually be diagnosed only by means of laparoscopy or laparotomy As it should be theoretically possible to identify malignancy involving the peritoneum by the demonstration of malignant cells in the peritoneal rinsing fluid, we filled the peritoneal cavity with fluid, as in peritoneal dialysis and allowed it to irrigate the abdominal wall for a while The fluid was then withdrawn and examined for the presence of malignant cells No report of a similar procedure appears to have been published

Material and Methods The clinical material consisted of 43 cases, thirteen of which had a malignant growth that had penetrated the peritoneal wall (diagnosed by surgery or autopsy), eleven had a growth with no apparent penetration of the peritoneal wall, ten had possible but unverified malignancy and nine cases had uraemia due to chronic renal disease

Submitted for publication 24 April 1969

Table

Cytologic findings in peritoneal rinsing fluid from 24 cases in various stages of abdominal malignancy — ten with possible abdominal malignancy and nine cases of uraemia

Cytologic findings in peritoneal rinsing fluid	Clinical or histologic diagnosis in 43 cases												
	Malignant tumour with penetration of peritoneal wall			Malignant tumour and no verified penetration of peritoneal wall			Possible malignant tumour unverified			Uraemia			
	+++	++	+	+++	++	+	+++	++	+	+++	++	+	
Malignant cells	3	2			—			—		2	1	0	8
Possibly malignant cells	1	1	1		—			—		1	0	0	4
Benign cells	1	0	4	1	2	8	2	0	8	0	2	3	31
	5	3	5	1	2	8	2	0	8	3	3	3	43

Profuse indicated by +++ moderate by ++ and sparse yield of cells by +

The peritoneal cavity was filled with 2 000 to 3 000 ml glucose sodium chloride solution approximately isotonic prepared for peritoneal dialysis The patient was then directed to walk about in the room and after 15 to 30 minutes an ordinary stilet catheter for peritoneal dialysis was inserted into the abdominal cavity The fluid was withdrawn the last half litre being sent immediately to the cytology laboratory The sample was marked only with the name and date of birth of the patient to ensure that the cytologic interpretation would not be influenced by clinical diagnosis

The fluid was centrifuged for ten minutes at 2 500 rpm Smears prepared from the deposit were fixed with Spraycyte fixative in aerosol form After staining by Papanicolaou s method the preparation was mounted with a cover glass and examined at a magnification of between 125 and 250 times The cell appearances were graded as benign possibly malignant and malignant and the cell counts as profuse moderate and sparse

Results

The number of cells identified in the rinsing fluid was profuse in eleven moderate in eight and sparse in twenty four cases Of thirteen cases with malignancy of the peritoneum malignant cells were demonstrated in five and

possibly malignant cells in three cases No malignant cells were present in the remaining five cases, including four with sparse counts

In the eleven cases of malignant growths in the abdomen not penetrating the peritoneum, and in the group with possible but not verified growths, no malignant or possibly malignant cells were observed Profuse to moderate numbers of inflammatory and mesothelial cells were demonstrated in six of the nine uraemic cases Atypical cells were noted in four cases and were assessed as malignant (three cases) or possibly malignant (one case), i e false positive findings

The results are summarized in the appended table

Conclusion

The technique enabled malignant or possibly malignant cells to be demonstrated in the rinsing fluid in eight out of thirteen cases of peritoneal carcinosis The sparse yield of cells in the rest of the carcinosis cases may have contributed to the poor accuracy A more profuse yield could possibly have been expected if the rinsing fluid had been allowed to remain longer in the peritoneal cavity This means using a rinsing fluid that is slowly absorbed and does not irritate the peritoneum or influence the cell appearances in any other way

The occurrence of false positive diagnoses among the uraemic cases was probably due to the fact that atypical mesothelial cells were erroneously assessed as malignant cells It is well known that many uraemic cases develop pericarditis or pleurisy, although the presence of peritonitis is probably more difficult to ascertain All the present cases had earlier undergone peritoneal dialysis with consequent mild peritoneal irritation The mesothelial cell reaction is thus explainable

Abdominal lavage would appear to cause little distress but if two or three litres of fluid, as used in the present procedure, are allowed to remain in the peritoneal cavity for some time, the effects may prove unpleasant

SUMMARY

Washing out of the peritoneal cavity with dialysis fluid and examining the rinsing fluid cytologically in 43 cases without ascites were undertaken with a view to establish if peritoneal carcinosis could be detected by this means The results indicate that malignant cells can be identified by this method but that there is a risk of false positive diagnosis in cases of uraemia

ZUSAMMENFASSUNG

Versuche mit Auswaschung der Peritonealhohle mit Dialysflussigkeit und zytologischer Untersuchung der Spulflussigkeit wurden in 43 Fallen ohne Aszites vorgenommen um peritoneale Karzinose zu entdecken Krebszellen konnen mit dieser Methode identifiziert werden aber in Fallen mit Uramie besteht die Gefahr eine falsch positive Diagnose zu erhalten

RÉSUMÉ

Les auteurs ont expérimenté une méthode de lavage de la cavité péritonéale avec le liquide de dialyse et ont examiné cytologiquement ce liquide de rinçage pour déceler une carcinose péritonéale sur 43 cas qui ne présentaient pas d'ascite. Les résultats montrent que cette méthode permet d'identifier les cellules malignes, mais qu'il y a un risque de résultats faussement positifs dans des cas d'urémie.

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Book review

RADIOLOGICAL PHYSICS Second edition By M E J Young 601 pages, 244 figures and numerous tables H K Lewis & Co, London 1967 Price £4 4s

The first edition of this book which appeared in 1957 has now been considerably enlarged and modernized It is however scarcely updated to its year of printing (1967) and a passage on p 254 relegates that part of the book to 1965 the references are mostly from the forties and fifties, with only a few from 1965—1966 and none from 1967 Some examples of recent development that have been omitted are mentioned below However for the stated purpose of the book (to serve as a textbook for student radiologists and radiographers as well as for physicists commencing hospital work) these deficiencies do not seem to be of serious consequence The value of the book for teaching basic radiologic physics is enhanced by a number of examination questions appended to most chapters

There are the usual introductory chapters on fundamental concepts and on various electronic devices The two chapters on the production of roentgen rays illustrate the general trend in allotting more than three quarters of the space to roentgen rays below 400 kV Chapters on radioactivity and on photon matter interaction follow traditional lines and seem to be quite adequate but a column on specific gamma ray constants is absent from the isotope table on pp 148—153 The reviewer has been unable to detect more than two such data in the whole book

Much the same may be said about the two chapters on the measurement of ionizing radiation, about the chapters on its therapeutic uses on the diagnostic uses of radioisotopes and on health hazards and protection The emphasis in the measurement chapters is on ion chambers and on various counting devices while calorimetric and chemical dosimeters are omitted (although the Fricke dosimeter is mentioned briefly later on) and thermoluminescent dosimeters are given only a page and a half The kerma concept is lacking although the considerations that led to its establishment are mentioned The therapeutic chapters include a number of instructive dose distribution diagrams for various treatment methods and descriptions of devices for e g beam direction but only manual dose planning methods are described Computer methods are omitted No simulator nor the use of roentgen TV methods (which appear only in the diagnostic chapter) are described Too little attention is paid to the advantages of electron beams and exciting new possibilities (energetic protons, negative π mesons neutrons) are left undiscussed The most common diagnostic radioisotope procedures are well covered but only half a page is given to the Anger gamma camera and other types are completely omitted The chapter on diagnostic roentgenology physics is good The most advanced chapter is perhaps the one on certain chemical and biologic radiation effects

The fact that the book is not altogether modern should not preclude it for teaching purposes it will certainly prove a useful handbook in less advanced routine work

Sten Benner

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